3.3 kcal mol^{-1}, which seems a little low. These results would seem to bear out the previous assumption[11,16] that $k_{-2} \approx k_3$ although they do not disprove our estimate of the Arrhenius parameters, since there is considerable uncertainty in these values and only a slight change in activation energies is required to make ring closure considerably faster than splitting of the biradical.

Conclusion

The results obtained by pyrolysis of cyclobutane under VLPP conditions have been shown to be compatible with previous data if high Arrhenius parameters are assumed. It has been shown that this assumption does not contravene any thermodynamic considerations. However, the VLPP data on gas-collision efficiency under these conditions cannot be reconciled with previous results, and at the present time we can suggest no valid reason for this discrepancy.[16a]

Appendix

The entropy (S_f^{723}) of cyclobutane at 723 K can be obtained from known values[15] at 700 and 800 K, and this agrees with the value obtained from the frequency assignment, as is shown in Table VI. The heat of formation (ΔH_f^{723}) can be calculated by adding the contribution due to $\int_{300}^{723} C_p dT$ to the known value at 300 K of 6.3 kcal mol^{-1}. S_f^{723} and ΔH_f^{723} for the biradical can be calculated by group additivity methods or from n-butane by making suitable corrections.[16,17] It must be remembered that since only singlet biradicals can participate in ring closure or ethylene formation, no correction for election spin degeneracy should be included in the above estimates. The results are shown in Table VI, and from these values we can obtain

$$\Delta H_2^{723} = \Delta H_f^{723}(\sqcup) - \Delta H_f^{723}(\square) = 59.60 \text{ kcal mol}^{-1}$$

and

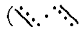
$$\Delta S_2^{723} = S_f^{723}(\sqcup) - S_f^{723}(\square) = 14.96 \text{ cal deg}^{-1} \text{ mol}^{-1}$$

These values lead to the value 1.3 × 10^{-14} for the equilibrium constant (K_2^{723}) for reactions 2 and -2.

The experimental value of the overall rate constant (k_∞) at 723 K is well known (Figure 3). If we assume $k_{-2} > k_3$ in the steady-state expression for k_∞, then we can make the approximation

$$k_\infty = \frac{(k_2/k_{-2})k_3}{1 + (k_3/k_{-2})} \cong K_2 k_3$$

and thus we can obtain an estimate of the upper limit for k_3. Since the entropy of the complex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is defined by the parameters shown in Table V, we can calculate $\Delta S_3^{\ddagger}$ and so $\log A_3^{\ddagger}$.

Ring closure in 1,2-dimethylcyclobutane appears to have an activation energy of about 7.4 kcal mol,[11,16] and from this limits of about $4 < E_{-2} < 6.6$ kcal mol^{-1} can be set[11,16] for the ring closure in cyclobutane. This higher value leads to an entropy of 7.0 cal deg^{-1} mol^{-1} ($\Delta S_{-3}^{\ddagger}$) and, since $\Delta S_2^{\ddagger} = \Delta S_2 + \Delta S_{-2}^{\ddagger} + R \ln 4$, we can calculate $\Delta S_2^{\ddagger}$, and thus $\log A_2^{\ddagger}$. The activation energy for reaction 2 can be calculated from the heat of formation of the biradical and the activation energy for ring closure. Thus we can estimate $\log k_2^{723}$ to be -3.57 and by combining this value with K_2^{723} we can obtain k_{-2}^{723} and thus $\log A_{-2}^{\ddagger}$. The values of $\log A_{-2}^{\ddagger}$ calculated by this method, and from $\Delta S_{-2}^{\ddagger} = 7.0$ cal deg^{-1} mol^{-1}, differ by only 0.2 log unit, which is well within experimental uncertainty.

(16a) Note Added in Proof. Some workers may conclude that the above results indicate that VLPP is not a useful technique. However, it must be emphasized that cyclobutane is the only species we have found to exhibit this behavior. The list of molecules studied by VLPP, for which the results agree with previously accepted (or expected) high-pressure parameters, now includes: isopropyl iodide, n-propyl iodide, ethyl acetate, azoisobutane, azoisopropane, azoethane, 2,3-dimethylbutane, 2,2,3,3-tetramethylbutane, *tert*-butyl peroxide, and *tert*-amyl peroxide.

(17) H. E. O'Neal and S. W. Benson, *Int. J. Chem. Kinet.*, 1, 221 (1969).

Quantitative Application of the Nuclear Overhauser Effect to the Determination of Molecular Structure

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Abstract: Procedures for obtaining relative internuclear distances from nuclear Overhauser effect measurements, particularly in three-spin systems, are described. Calculations for model systems and for real systems using literature data are given.

The nuclear Overhauser effect (NOE) is the change in the integrated intensity of one line in an nmr spectrum when a strong radiofrequency field is applied at the frequency of a second resonance in the spectrum. In spin systems that relax primarily through intramolecular dipole–dipole interactions, the NOE has a $1/r^6$ dependence on the internuclear distance. Because of this dependence on internuclear distances, the NOE has found application in organic structural chemistry.[1] These applications have generally been of a qualitative nature, although the potential of the NOE for quantitative determination of relative internuclear distances has been recognized.[2]

In this paper, explicit expressions relating the observed NOE's to internuclear distances for several common spin groupings are presented. These relations are then used to calculate the NOE as a function of geometry for several model systems in order to demonstrate several features of the Overhauser effect which are of particular significance in attempting a qualitative interpretation of NOE data in terms of molecular structure. Finally, a few examples of the application of the equations will be presented using data from the literature.

Theory

The NOE may be discussed most conveniently in terms of $f_d(s)$, the fractional change in the area under resonance d when a resonance or set of resonances s is saturated.[3] Under conditions that are generally satisfied by organic systems it can be shown that[1,2]

$$f_d(s) = \sum_s \frac{\gamma_s \rho_{ds}}{2\gamma_d R_d} - \frac{1}{2\gamma_d R_d} \sum_{n \neq d,s} \gamma_n \rho_{dn} f_n(s) \qquad (1)$$

where

$$R_d = \sum_i \rho_{di} + \rho_d^*$$

and

$$\rho_{ij} = \gamma_i^2 \gamma_j^2 \tau_c(ij)/r_{ij}^6$$

In these equations γ_i is the gyromagnetic ratio of nucleus i, r_{ij} is the distance between nuclei i and j, and $\tau_c(ij)$ is the correlation time for reorientation of the vector connecting spins i and j. R_d is the total rate of the relaxation of spin d; it is given by the sum of the rates due to intramolecular dipole–dipole interactions with spins n, ρ_{dn}, and due to all other relaxation mechanisms, ρ_d^*. The main contributions to ρ_d^* are normally from dipole–dipole interactions with solvent spins, lock sample, or dissolved paramagnetic species; quadrupole, spin rotation, and other mechanism are also lumped into ρ_d^* when they are present. The only restriction on the validity of eq 1 that we need mention here is that it is not applicable to tightly coupled spin systems or to spins which are undergoing chemical exchange.

The internuclear distances enter into eq 1 quite directly through the $1/r^6$ dependence of ρ and thus the NOE is capable of giving information on molecular geometry. However, the naive assumption that the closer the spins, the larger the NOE observed can frequently be misleading because (a) the NOE depends upon the total spin–lattice relaxation rate R_d and this quantity will not be the same for all spins, and (b) the second term of eq 1, which represents the indirect polarization of spin d by s through the other spins n, will alter the NOE in a manner which is not immediately obvious. The only accurate generalization is that the enhancement of the d resonance will depend upon the *relative* proximity of d to the spins s and n. The explicit expressions for the NOE in simple systems which will be presented below, and the calculations using those expressions, will make the nature of the dependence of the NOE on the relative spin positions more clear.

Two Nonequivalent Spins: AX. In the case when there are only two types of spins, A and X, present, eq 1 simplifies to

$$f_d(s) = \frac{\gamma_s}{2\gamma_d} \frac{\rho_{ds}}{\rho_{ds} + \rho_d^*} \qquad (2)$$

It is apparent from this equation that a 50% enhancement of the observed signal is the maximum that can occur in a homonuclear NOE experiment and that the maximum value will be obtained only when $\rho_d^* \ll \rho_{ds}$. It is also apparent from eq 2 that the reason NOE's are not generally observed between distant spins is not their separation *per se* but rather that ρ_d^* is generally much larger than ρ_{ds} under that condition.

Three Nonequivalent Spins: AMX. A system of three nonequivalent, loosely coupled spins is the simplest case for which information on molecular geometry is directly available from steady-state experiments. Six experiments are possible between the three spins in this case. Equation 1 may be written for two of these experiments as

$$f_X(M) = \frac{\gamma_M}{2\gamma_X} \frac{\rho_{MX}}{R_X} - \frac{\gamma_A}{2\gamma_X R_X} \rho_{AX} f_A(M) \qquad (3a)$$

$$f_A(M) = \frac{\gamma_M}{2\gamma_A} \frac{\rho_{AM}}{R_A} - \frac{\gamma_X}{2\gamma_A R_A} \rho_{AX} f_X(M) \qquad (3b)$$

These equations may then be solved simultaneously to obtain a closed expression for $f_A(M)$ in terms of the ρ's and R's.

$$f_A(M) = \frac{\rho_{AX}\rho_{MX} - 2R_X\rho_{AM}}{\rho_{AX}\rho_{XA} - 4R_A R_X} \qquad (4)$$

Using $\rho_{ij} \propto 1/r_{ij}^6$ in eq 4 allows one to calculate the enhancements that would be expected for any arrangement of the three spins in space.

Assuming that $\tau_c(AX) = \tau_c(AM)$, which is a reasonable assumption for all but very small or very asymmetrical molecules, eq 1 can be rewritten for three spins as

$$\left(\frac{r_{AX}}{r_{AM}}\right)^6 = \frac{\gamma_X^3 f_A(M) + f_A(X) f_X(M)}{\gamma_A^3 f_A(X) + f_A(M) f_M(X)} \qquad (5)$$

Providing all the necessary enhancements can be measured, eq 5 allows one to calculate the *ratio of the internuclear distances* from the enhancements. The fact that only the ratio of distances and not their absolute values is obtained from NOE experiments is very significant: it again shows that the relative position of the spins and not the actual magnitude of their separation is what determines the observed NOE. Another important point shown in eq 5 is that, if the location of spin A is sought, the most important NOE's will be those for which A is observed and not those for which A is saturated.

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(1) J. H. Noggle and R. E. Schirmer, "The Nuclear Overhauser Effect: Chemical Applications," Academic Press, New York, N. Y., in press.

(2) R. E. Schirmer, J. H. Noggle, J. P. Davis, and P. A. Hart, *J. Amer. Chem. Soc.*, **92**, 3266 (1970); R. A. Bell and J. K. Saunders, *Can. J. Chem.*, **48**, 1114 (1970).

(3) In ref 2, $f_d(s)$ was written f_s^d. Similarly, ρ_s^d was written for ρ_{ds} and ρ_{other}^d for ρ_d^*. The notation used in the current paper follows that of ref 1.

Equivalent Spins: AX_2.[4] In discussing groups of equivalent spins it is necessary to distinguish the various nuclei within the group; the two nuclei in the X_2 grouping will, therefore, be labeled X′ and X″. We will assume that $\rho_{AX'} = \rho_{AX''}$, or at least that their average values are equal. The enhancement of A when X is saturated is then obtained directly from eq 1 as

$$f_A(X) = 2\left(\frac{\gamma_X}{2\gamma_A}\right)\frac{\rho_{AX}}{R_A} \tag{6}$$

The factor 2 arises because the equivalence of X′ and X″ requires that both be saturated if one of them is saturated. Note that the maximum enhancement is $f_A(X) = 0.50\gamma_A/\gamma_X$, just as it would be if X were a single spin rather than a group of equivalent spins. This follows from the fact that $R_A = \rho_{AX'} + \rho_{AX''} + \rho_A{}^*$ so that $R_{A,\min} = 2\rho_{AX}$.

To calculate $f_X(A)$, we write eq 1 for $f_{X'}(A)$ and then use the equalities

$$f_{X'}(A) = f_{X''}(A) \equiv f_X(A)$$

and

$$R_{X'} = \rho_{X''X'} + \rho_{X'A} + \rho_{X'}{}^*$$

The resulting equation can be solved to obtain

$$f_X(A) = \frac{\gamma_X}{2\gamma_A}\,\frac{\rho_{AX}}{{}^3/_2\rho_{X'X''} + \rho_{AX} + \rho_X{}^*} \tag{7}$$

Two Groups of Equivalent Spins: A_NX_M. Using the same general proedure as was used for the AMX and AX_2 cases, it can be shown that

$$f_A(X) = \frac{\gamma_X}{2\gamma_A}\,\frac{M\rho_{AX}}{{}^3/_2(N-1)\rho_{AA} + M\rho_{AX} + \rho_A{}^*} \tag{8}$$

Equation 8 again requires that all ρ_{AX} be equal on the average. The equation for $f_X(A)$ is exactly analogous to that for $f_A(X)$ and can be obtained from it by interchanging X and A and M and N wherever they appear. An examination of the equations for $f_X(A)$ and $f_A(X)$ shows that analogs of the three-spin equation (5) do not exist for systems containing only two types of spin. This means that steady state experiments alone cannot determine internuclear distances in these systems.

Four Nonequivalent Spins: AGMX. For four nonequivalent, loosely coupled spins, the following relation can be obtained.

$$\left(\frac{r_{GM}}{r_{AM}}\right)^6 = \frac{\gamma_G{}^3}{\gamma_A{}^3} \times \frac{\begin{array}{l} f_M(A) + f_M(G)f_G(A) + f_M(X)f_X(A) + \\ \quad f_M(G)f_G(X)f_X(A) + f_M(X)f_X(G)f_G(A) - \\ \qquad f_M(A)f_G(X)f_X(G) \end{array}}{\begin{array}{l} f_M(G) + f_M(A)f_A(G) + f_M(X)f_X(G) + \\ \quad f_M(A)f_A(X)f_X(G) + f_M(X)f_X(A)f_A(G) - \\ \qquad f_M(G)f_A(X)f_X(A) \end{array}} \tag{9}$$

If all terms other than the first two in the numerator and the first two in the denominator are deleted from this expression, the three-spin formula remains. Comparing eq 5 and 9 shows how rapidly the complexity of the closed expressions increases with increasing number of spins. As the number of spins increases, numerical procedures based on eq 1 become desirable alternatives to the use of closed formulas such as eq 9.

The AMX_3 Case. Equation 1 can be solved[1] for the spin system AMX_3 in the case where ρ_{AX} and ρ_{MX} are the same (at least on the average) for all of the X spins. We obtain

$$\frac{\rho_{AM}}{3\rho_{AX}} = \frac{\gamma_X}{\gamma_M}\,\frac{f_A(M) + f_A(X)f_X(M)}{f_A(X) + f_A(M)f_M(X)} \tag{10}$$

The factor of 3 occurs because, by the convention of ref 1 and the definition following eq 1 of this paper, ρ_{AX} is the spin-lattice relaxation parameter of spin A due to a *single* spin X; thus $3\rho_{AX}$ is the relaxation of A due to all three equivalent spins X.

The ratio ρ_{AX}/ρ_{MX} will be given by the same equation (eq 5) as the AMX case since the factor of 3 will cancel.

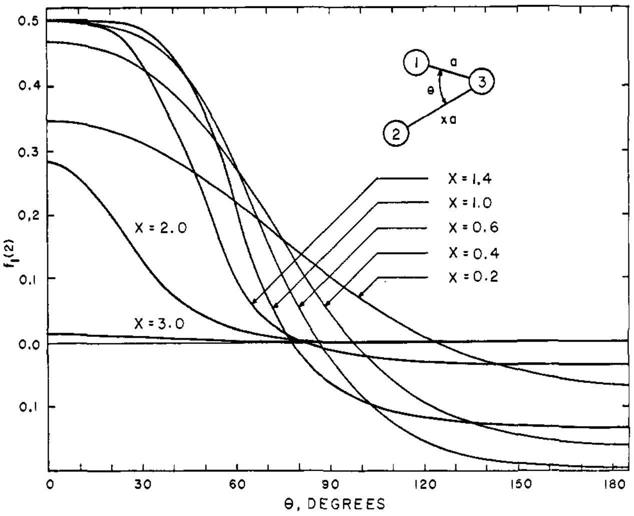

Figure 1. The nuclear Overhauser effect as a function of the relative positions of the spins in a three-spin system. The curves represent the enhancement of the resonance of spin 1 when the resonance of spin 2 is saturated and intermolecular relaxation is negligible. The magnitude of the distance *a* does not enter the calculation as the NOE depends only on the *relative* internuclear distances.

Calculations on a Model System

The geometry of a group of three spins can be completely specified by an angle θ and two distances, a and xa, as shown in Figure 1. The enhancement of the resonance of spin 1 when the resonance of 2 is saturated can be expressed directly in terms of θ and x by using eq 4 and a little trigonometry. The result is

$$f_1(2) = \frac{x^{-6} - 2(1 + x^{-6})(1 + x^2 - 2x\cos\theta)^{-3}}{1 - 4(1 + x^{-6}) - 4(1 + x^{-6})(1 + x^2 - 2x\cos\theta)^{-3}} \tag{11}$$

In writing this equation it has been assumed that intermolecular relaxation (ρ^*) as well as interactions of 1, 2, and 3 with any other spins that might be present in the molecule are all negligible. Plots of $f_1(2)$ *vs.* θ calculated using eq 11 are shown in Figure 1 for several values of x. Several particularly significant features of these plots are as follows.

(a) $f_1(2)$ is large and positive when 1 is closer to 2 than it is to 3, as is the case when θ is small and x is close to 1.0.

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[4] A more detailed discussion of equivalent spins will be given in ref 1.

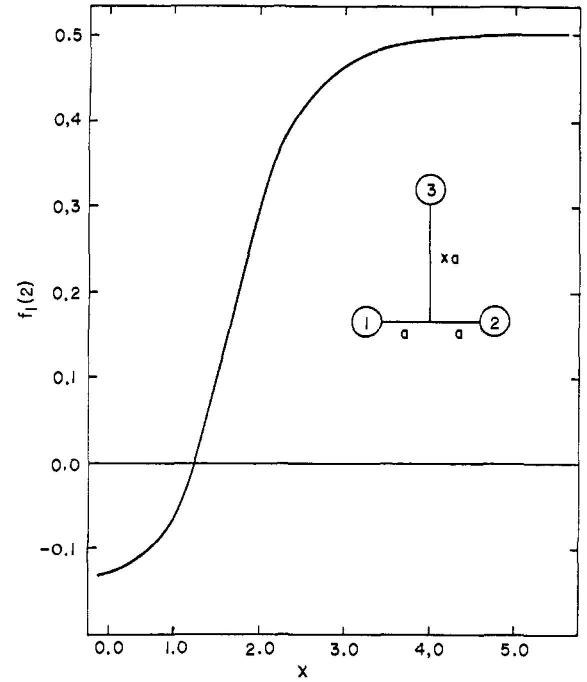


Figure 2. The effect of the position of a third spin upon the enhancement of the resonance of 1 when the resonance of 2 is saturated.

(b) As x increases beyond 2.0, the distance between 1 and 2 becomes larger than the distance between 1 and 3, and $f_1(2)$ rapidly decreases for *all* values of θ; by the time $x = 3$, a small positive enhancement still occurs in the region of $\theta = 0$, but $f_1(2)$ is zero everywhere else.

(c) When 3 lies between 1 and 2 ($\theta \gtrsim 90°$), the saturation of 2 results in a negative enhancement (decrease in signal area) of the resonance of 1. This is the effect first reported by Bell and Saunders.[5]

(d) Regardless of the value of x, there exists an angle at which $f_1(2) = 0$. The distance between spins 1 and 2 is not necessarily large at this angle. For example, $f_1(2) = 0$ at approximately $x = 1.0$ and $\theta = 77°$. The distances between the spins in this configuration are $r_{12} = 1.25$ Å and $r_{23} = r_{13} = 1.0$ Å if a is taken as 1.0 Å.

The dependence of $f_1(2)$ on geometry may be seen more clearly in the special case shown in Figure 2. We again set $\rho^* = 0$ for all spins. In this case, spin 3 is constrained to lie on the perpendicular bisector of the line joining spins 1 and 2, so that its position on the bisector is the only variable with the 1–2 distance remaining constant. Again, negative enhancements are calculated when 3 lies "between" 1 and 2. As 3 moves farther away, the enhancements become more positive, passing through zero at $x = 1.25$ and then approaching 0.50 asymptotically as $x \rightarrow \infty$. Figures 1 and 2 again make it very clear that the observed NOE is a result of the relative position of all interacting spins rather than simply the distance between the irradiated and observed spin.

A three-spin example of practical importance is the enhancement of the resonance of methylene protons when the resonance of a single proton on an adjacent carbon is saturated. The results are shown in Figure 3. It has been assumed that there are no other interacting spins in the molecule, that the intermolecular contribution to the relaxation of 1 and 3 is negligible, and, of course, that the spins are loosely coupled. Curve A in Figure 3 represents the enhancement of 1 when 2 is saturated and assuming that 1 and 3 are nonequivalent spins. A plot of $f_3(2)$ *vs.* θ would be identical with curve A except for being displaced horizontally by +120°.

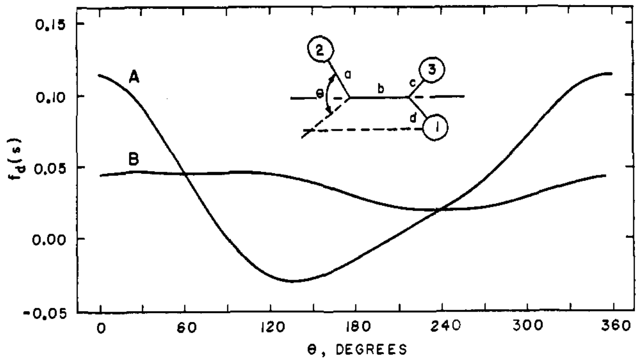
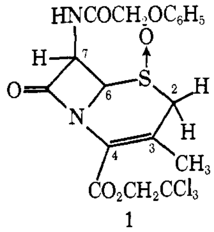


Figure 3. The enhancement of the resonance of methylene protons upon saturating the resonance of an adjacent methine proton. The bond lengths used in the calculation were $a = d = c = 1.12$ Å and $b = 1.54$ Å. (A) The enhancement of 1 when 2 is saturated, assuming 1 and 3 are nonequivalent and loosely coupled. (B) The enhancement of the resonance of 1 and 3 when 2 is saturated and 1 and 3 are equivalent.

However, curve A is unrealistic because 1 and 3 will usually be either equivalent or nonequivalent and tightly coupled. In either case, the enhancement expected would be given by curve B [the sum of $f_1(2)$ and $f_3(2)$], providing the enhancement of the entire AB spectrum is used as a measure of the NOE in the tightly coupled case. It can be seen that NOE experiments between equivalent or nearly equivalent geminal methylene protons and protons on adjacent, directly bonded carbons will not be useful for determining the H-C-C-H dihedral angle because (a) the enhancement is relatively independent of the dihedral angle and (b) the enhancements and changes in enhancements are of approximately the same magnitude as the error in the experiment, which is ±0.03 at best. This would appear to confirm the explanation offered by Cooper, *et al.*,[6] for their inability to assign the AB spectrum of the 2-CH_2 protons in Δ^3-deacetoxycephalosporin sulfoxide (1) on



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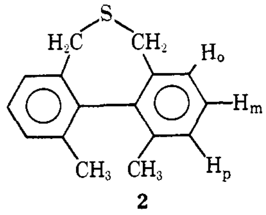

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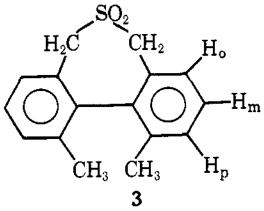

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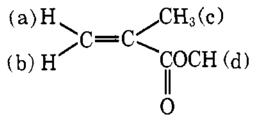

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[5] R. A. Bell and J. K. Saunders, *Can. J. Chem.*, 46, 3421 (1968).

[6] R. D. G. Cooper, P. V. DeMarco, C. F. Murphy, and L. A. Spangle, *J. Chem. Soc. C*, 340 (1970).

the basis of NOE experiments between the 2-CH_2 and 3-CH_2 proton resonances.[7] Similar results would be found for cases where a methyl resonance was observed while an adjacent proton was saturated.

Applications

The NOE data on 1,11-dimethyl-5,7-dihydrodibenz-[*c,e*]thiepin (**2**) and 1,11-dimethyl-5,7-dihydrodibenz-[*c,e*]thiepin *S*-dioxide (**3**) reported by Fraser and Schuber[8] are recorded in Table I. The ratio r_{12}/r_{1o} may be calculated using the data from Table I in eq 5.

Table I. NOE Data on Compounds **2** and **3**[a,b]

	Compd **2**	Compd **3**
$f_1(o)$	0.08	0.10
$f_2(o)$	−0.05	−0.01
$f_2(1)$	0.47	0.48
$f_o(1)$	0.23	0.21
$f_1(2)$	0.40	0.30
$f_o(2)$	−0.05	0.00

[a] Measurements were made on solutions of less than 5% (w/v) concentration in deuterated dimethyl sulfoxide. Both **2** and **3** were deuterated in the meta position for these studies. [b] Data from ref 8. The resonance of the two equivalent aromatic protons ortho to the benzylic groups is labeled "o." The two geminal protons on each benzylic -CH_2- group are nonequivalent. One proton from each benzylic -CH_2- occurs under resonance 1 and the other under resonance 2.

compound **2** $\quad r_{12}/r_{1o} = 0.73 \pm 0.12$

compound **3** $\quad r_{12}/r_{1o} = 0.83 \pm 0.06$

The error in these distance ratios was estimated from eq 5 with the assumption that the uncertainty in each measured enhancement is δ, where δ is independent of the magnitude of the enhancement. The result is

$$\Delta(r_{12}/r_{1o}) \approx \frac{(r_{12}/r_{1o})\delta}{6} \times \left[\frac{1 + f_1(2) + f_2(o)}{f_1(o) + f_1(2)f_2(o)} - \frac{1 + f_1(o) + f_o(2)}{f_1(2) + f_1(o)f_o(2)}\right]$$

Fraser and Schuber indicated that $\delta = \pm 0.05$ so that, using the values in Table I, the error in the ratios is as indicated.

An approximate check on these values was made by constructing a model of **2** using a Framework Molecular Model Set (Prentice-Hall). The C–S bond length was taken as 1.81 Å. The value of the ratio obtained from this model was 0.75, in excellent agreement with the value calculated from the NOE data. The value of the ratio in **3** calculated from the experimental data is larger than the ratio in **2** by an amount just barely outside the expected error limits. This might reflect a small difference in geometry between the two molecules, although C–S bond lengths decrease by only a few hundredths of an ångström in proceeding from sulfides to sulfoxides and then sulfones.[9–16] The question of such small conformational differences is probably best answered by methods of higher accuracy than NOE.

Another three-spin example is afforded by the data of Fukumi, *et al.*,[17] on methyl methacrylate (**4**). Their data are presented in Table II. This example is complicated by the fact that resonance *c* is that of a methyl group and nothing is known about the rotation of the methyl group about its axis. Equation 10 can be used to obtain

Table II. NOE Data on Compound **4**[a,b]

	Observed			
Irradiate	*a*	*b*	*c*	*d*
a		0.00	0.00	0.00
b	0.42		0.00	0.00
c	0.09	0.01		0.00
d	0.00	0.00	0.00	

[a] The NOE enhancements were measured on a 10% solution of **4** in carbon disulfide. [b] Data from Fukumi, *et al.*, ref 17.

$$\rho_{ab}/\rho_{ac} = 13.38$$

If we then assume $\tau_c(ab) = \tau_c(ac)$ and $r_{ab} = 1.84$ Å (measured on a Framework Molecular Model), we find

$$\langle r_{ac}^{-6}\rangle^{-1/6} = 2.83\ \text{Å} \qquad (12)$$

where the angular brackets indicate the average of r_{ac}^{-6} over all positions the methyl group can assume about its axis. If the methyl group is assumed to take on all orientations about its axis with equal probability, the "distance" (as defined by eq 12) between any one of the methyl protons and H_a is 2.88 Å, where the average has been computed by measuring internuclear distances on a molecular model for 13 equally spaced values of the angle about the methyl axis and then using a Simpson's rule integration to evaluate the average. The agreement between the values for $\langle r_{HC}^{-6}\rangle^{-1/6}$ derived from the NOE data and from measurements on molecular models is surprisingly good, but it is not possible to say at this time whether or not agreement will occur often enough for this type of approximation to be useful in studies of molecular structure. The assumption of equal correlation times for all the interactions (*ac*, *ab*, and *bc* in this example) depends upon the rate of rotation of the methyl group being less than or equal to the rate of molecular tumbling, and this will not be true for methyl groups in large molecules. However, the sixth power dependence of NOE enhancements on distance is so strong that assumptions of this type will often introduce only minimal errors.

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(7) The footnote in ref 6 stating that the mutual relaxation of the methylene protons could be removed by irradiating at the center of gravity of one-half of the AB quartet is in error. While saturating the methyl resonance and half of the AB quartet simultaneously would be expected to result in a rather large enhancement of the other half of the quartet, this in no way reflects a change in the efficiency of the mutual relaxation of the methylene protons.

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Conclusion

Explicit expressions have been presented for calculating internuclear distances from NOE data. In addition, several conclusions can be drawn from the quantitative theory which are of value even when the enhancements can be used in only a qualitative manner. Some of these are as follows.

1. A zero NOE does *not necessarily* imply that the two spins are distant. It can be due to a cancellation of the direct and indirect ("three-spin") effects.

2. The relative values of the *enhancements of A*, $f_A(i), f_A(j), \ldots$, when the other spins $i, j, \ldots$ are saturated are a much better indication of the position of A with respect to those other spins than are the relative enhancements of the other spins when A is saturated.

3. If $f_A(m)$ and $f_A(x)$ are the *only* large enhancements of spin A, then

$$\frac{r_{ax}}{r_{am}} \approx \left(\frac{f_A(m)}{f_A(x)}\right)^{1/6}$$

This is, at least, a good way to get first approximations.

4. If the NOE between two spins is negative, another spin lies more or less between them. This conclusion is, however, only valid in the absence of chemical exchange effects.

5. Indirect effects through rapidly relaxing spins or groups of spins are small. Thus methyl groups or quadrupolar nuclei will not give large "three-spin" effects.

6. NOE enhancements are sensitive only to *relative* distances and the size of ρ^*. Large values of $f_i(j)$ and $f_j(i)$ imply only that i and j are closer to each other than to other spins. Large values of ρ^* will result in small NOE's but will not destroy the dependence of the NOE's on distance ratios.

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An Atom Dipole Interaction Model for Molecular Polarizability. Application to Polyatomic Molecules and Determination of Atom Polarizabilities

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Abstract: The Silberstein model for molecular polarizability is applied to polyatomic molecules. The atoms are regarded as isotropically polarizable points located at their nuclei, interacting *via* the fields of their induced dipoles. The theory is restated in a simple exact form suitable for numerical calculation of molecular polarizability tensors. The use of additive values for atom polarizabilities gives poor results, in some cases leading to artificial predictions of absorption bands. The theory is used to determine optimum polarizabilities of H, C, N, O, F, Cl, Br, and I in 41 different molecules including alkanes, alcohols, ethers, halomethanes, aldehydes, ketones, amides, and nitriles. The atom polarizabilities found are significantly smaller than the additive values in most cases. Using the new values, the agreement between calculated and experimental mean molecular polarizabilities is usually within 1–5%. Agreement for polarizability components is generally poorer but consistent with the view that molecular anisotropy originates to a large extent from atom dipole interactions.

It is often desirable to know the polarizabilities of various parts of a molecule, such as the atoms, bonds, or functional groups. This information enables one to predict total molecular polarizabilities and other interesting molecular properties, such as optical rotation[1] and London dispersion forces between parts of molecules.[2] A view which has prevailed for some time is that the polarizability of a molecule is simply the sum of the polarizabilities of its parts.[3] This is based on the finding that the molar refraction, which is proportional to the molecular polarizability, is an additive property; that is, the various atoms or functional groups in a molecule can be assigned refraction values whose sum for the whole molecule is the molar refraction, and the value for a given group or atom is fairly constant for a variety of molecules. Extensive tables of additive atom and group refractions are available.[3,4] The additivity hypothesis has been extended in the interpretation of anisotropy of polarizability;[5,6] thus polarizability tensors have been ascribed to various bonds and functional groups according to the hypothesis that componentwise addition of the group tensors gives the molecular polarizability tensor. Compilations of bond tensor data have been given by Denbigh[5] and LeFèvre and LeFèvre.[6]

However, the additivity hypothesis has been repeatedly criticized[2,7,8] on the grounds that it neglects the interactions among the groups in a molecule, such

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