APPLICATIONS OF THE INTRAMOLECULAR NUCLEAR OVERHAUSER EFFECT IN STRUCTURAL ORGANIC CHEMISTRY

GARY E. BACHERS AND T. SCHAEFER*

Department of Chemistry, University of Manitoba, Winnipeg, Manitoba, Canada

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Contents

I. Introduction

A. SCOPE OF THE REVIEW

In the past few years the intramolecular nuclear Overhauser effect has become a vital technique in structural organic chemistry.[1] In this article we attempt to present a coherent summary of the theory and of the applications of this phenomenon to this area of chemistry. The theoretical background is described at an unsophisticated level but in enough detail so that the organic chemist can appreciate the origin of the phenomena he observes. Numerous pertinent examples from the literature are described, but a really comprehensive coverage is not attempted. We apologize to those authors whose work is not mentioned; no judgment of scientific merit is intended.

There are numerous applications of the general Overhauser effect to problems in physical chemistry, but such studies are here mentioned only in passing. The famous article on double resonance phenomena by Hoffman and Forsén[2] should be consulted by those readers interested in a fundamental and extensive discussion of the general Overhauser effects.

B. DEVELOPMENT OF THE FIELD

The original Overhauser effect, as described by Overhauser in 1953,[3] involves electronic/nuclear cross-relaxation processes. The first nuclear Overhauser effect was described by Solomon[4] in 1955 and by Solomon and Bloembergen in 1956.[5] This is the nuclear/nuclear analog of the original effect. The first intermolecular nuclear Overhauser effect in a strictly protonic system was reported by Kaiser in 1965.[6] Kaiser studied intermolecular cross-relaxation effects in the mutual interaction of chloroform and cyclohexane. Anet and Bourn[7] in the same year reported the first proton intramolecular nuclear Overhauser effect. These authors predicted that "studies of NOE's. . .should be of considerable stereochemical and conformational interest in organic chemistry."

C. GENERAL DESCRIPTION OF THE TECHNIQUE

The experimental technique involved in the observation of intramolecular nuclear Overhauser effects (nOe's) is similar to that used in other double resonance studies.[1] One of the protons or groups of protons is irradiated at its resonance frequency while the spectrum is observed by means of a frequency sweep. Intensity changes in the peaks of a high-resolution nuclear magnetic resonance (nmr) spectrum are caused by changes in the populations of the eigenstates of the spin Hamiltonian, *i.e.*, of the energy levels of the nuclear Zeeman levels. If a molecule contains two protons A and B so placed that only A is involved in the relaxation process of B and *vice versa*, then the saturation of B will result in an increase in the integrated signal of A by 50% and *vice versa*. Thus, one saturates a given proton or group of protons and observes the nmr spectrum of the molecule. An increase in the integrated area of some other peak(s) in the spectrum indicates the presence of an nOe. Intramolecular nOe's lead to qualitative structural information and also to information on internuclear distances.[8] The nuclear Overhauser effect makes it possible to determine which protons are in close molecular proximity but which need not be spin–spin coupled. An example of the experimental technique and its pitfalls is given by Bell and Saunders.[8]

The observation of nOe's involves a consideration of the intramolecular spin-lattice relaxation paths for the various protons in a molecule. The relaxation time T_1 is used to express the efficiency of relaxation from a higher to a lower energy nuclear spin state, this parameter being strongly affected by the presence of paramagnetic ions or molecules, so that investigations of nOe's must be done using magnetically inert solvents, thus minimizing intermolecular contributions to the relaxation mechanism by dipole–dipole interactions.

Two phenomena known as "general nOe's" have been observed and are not dependent on cross-relaxation. The first involves a redistribution of the intensities of the peaks of a proton which occurs when one peak of a multiplet of another proton is saturated.[9,10] The second phenomenon involves a decrease in the intensity of a proton peak when another peak of the same proton is saturated, provided the proton reso-

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[1] P. D. Kennewell, *J. Chem. Educ.*, **47**, 278 (1970).

[2] R. A. Hoffman and S. Forsén, *Progr. Nucl. Magn. Resonance Spectrosc.*, **1**, 35 (1966).

[3] A. W. Overhauser, *Phys. Rev.*, **91**, 476 (1953).

[4] I. Solomon, *ibid.*, **99**, 559 (1955).

[5] I. Solomon and N. Bloembergen, *J. Chem. Phys.*, **25**, 261 (1956).

[6] R. Kaiser, *ibid.*, **42**, 1838 (1965).

[7] F. A. L. Anet and A. J. R. Bourn, *J. Amer. Chem. Soc.*, **87**, 5250 (1965).

[8] R. A. Bell and J. K. Saunders, *Can. J. Chem.*, **48**, 1114 (1970).

[9] W. A. Anderson and R. Freeman, *J. Chem. Phys.*, **37**, 85 (1962).

[10] R. Kaiser, *ibid.*, **39**, 2435 (1963).

nance splitting is caused by spin coupling to a nucleus having a relaxation time comparable to that of the proton.[11,12]

II. Theoretical Considerations

The discussion approximately follows that of Bell and Saunders.[8] Many factors contribute to T_1, including intramolecular effects, such as neighboring dipoles, anisotropic bonds, and time-dependent scaler spin–spin interactions, and intermolecular effects such as paramagnetic species, external dipoles, and fluctuating magnetic fields. T_1 can be computed from

$$1/T_1 = 1/T_a + 1/T_b + 1/T_c + \ldots$$

where T_a, T_b, and so on are contributions of each type of relaxation mechanism possible. However, it is often found that the dipole–dipole interaction[13] between a given proton and its nearest neighbors in an organic molecule is the main intramolecular contribution to T_1. This, of course, presupposes that the molecule is not undergoing chemical exchange. In the following a dipole–dipole interaction is assumed.

Consider now two sets A and B of weakly interacting protons in an external magnetic field, H_z. Assume that a Boltzmann distribution among the spin states has been attained. The equilibrium magnetizations, M_0^A and M_0^B, are proportional to the population differences between the spin states, and it is convenient to consider their behavior under nonsteady-state conditions, brought about by perturbations. Let M_z^A and M_z^B be the instantaneous magnetizations of A and B. Under steady-state conditions, *i.e.*, when the populations of the spin states do not change in time

$$\mathrm{d}M_z/\mathrm{d}t = 0 \qquad (1)$$

More generally, after a perturbation which upsets the equilibrium is removed, the magnetizations will relax back toward equilibrium at rates determined by the spin-lattice relaxation times, T_1. One may write[4,8,14] the rate equations

$$\mathrm{d}M_z^A/\mathrm{d}t = -(M_z^A - M_0^A)/T_{AA} - (M_z^B - M_0^B)/T_{BA} \qquad (2)$$

$$\mathrm{d}M_z^B/\mathrm{d}t = -(M_z^B - M_0^B)/T_{BB} - (M_z^A - M_0^A)/T_{AB} \qquad (3)$$

In these equations T_{AA} is the total of the intermolecular and the intramolecular contributions to T_1 of the A protons and T_{BA} is the contribution to T_1 of the A protons caused by the interaction of A and B protons; similarly for T_{BB} and T_{AB}. By definition T_{AB} and T_{BA} are equal.

If the resonance of A is saturated (the strong rf field equalizes the populations of the A levels), $M_z^A = 0$, and when a steady state is reached under these conditions application of eq 1 to eq 3 results in

$$M_z^B = M_0^B + M_0^A T_{BB}/T_{AB} \qquad (4)$$

Equation 4 means that the intensity of the resonance from B *increases* by $M_0^A T_{BB}/T_{AB}$. It can be shown[14] that $T_{BB}/T_{AB} = {}^1/_2$ for two interacting magnetic dipoles A and B of the same spin, and hence the maximum increase in the B signal is 50%. This conclusion holds for nonviscous solutions, *i.e.*, for most common organic solvents near room temperature.

Competing relaxation mechanisms will cause a decrease in the value of 50% and can arise from magnetic nuclei in the solvent, for example, or from dissolved oxygen. The latter can be removed by degassing the sample tube, and offending protons in the solvent molecules can be replaced by deuterons, which are much less effective as agents for relaxation by dipole–dipole mechanisms.

Because the magnetic field from the nuclear dipole varies as r^{-3}, where r is the distance from the dipole, it is reasonable that the nOe depends strongly on the distance between the A and B protons. In fact, the enhancement of the intensity turns out to be proportional to the inverse sixth power of the distance between the A and B protons, r_{AB}^{-6}. In this way the power of the method in locating spatially proximate protons (or other nuclei) in a molecule becomes evident. Clearly, a qualitative application in the determination of the configuration of *rigid* organic molecules is easy in principle.

When the molecule is conformationally *mobile*, the occurrence of an nOe is not sufficient evidence for the time-independent proximity of two protons.[15] The only allowed conclusion is that two sets of nuclei are located in each other's vicinity for a period of time. Variable-temperature nOe measurements may still provide more definite inferences in such cases.[15]

Under certain somewhat stringent conditions of solute concentration, solvent properties, and shapes of solute molecules, Bell and Saunders[8] conclude that when r_{AB} is less than a critical value, r^0, the nOe approaches the limiting value of $^1/_2$. When $r_{AB} > r^0$ they suggest

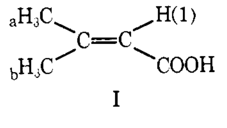
$$\mathrm{nOe} = 1/Ar_{AB}^6 \qquad (5)$$

where A is a constant. For a series of molecules in which single proton–proton distances could be measured, they found excellent agreement with eq 5, which also gave agreement for interactions between a proton and methyl protons. One may demure at their method of measuring the internuclear distance in the latter instance. What is perhaps more surprising is that the ratio of the times which characterize the rotational and translational motion of the molecule containing the protons is evidently the same for molecules of widely different shapes and sizes.

Negative nOe effects are observed in a system of four neighboring spins.[16] By considering equations similar to eq 2 and eq 3, this observation can be rationalized if dipole–dipole relaxation is dominant.

III. Applications to Organic Chemistry

Anet and Bourn[7] in their pioneering work on nOe's studied the compound β,β-dimethylacrylic acid (I). They found that



I

irradiation of the high-field methyl groups resulted in a H(1) signal of relative intensity 117 ± 1 while irradiation of the low-field methyl group gave an H(1) signal of relative intensity 96 ± 1, and thereby concluded that the upfield methyl group is cis to H(1) since it contributed more to the relaxation of H(1) and was therefore in greater proximity to that

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(11) K. Kuhlman and J. D. Baldeschwieler, *J. Amer. Chem. Soc.*, **85**, 1010 (1963).

(12) F. A. L. Anet, *Tetrahedron Lett.*, 3399 (1964).

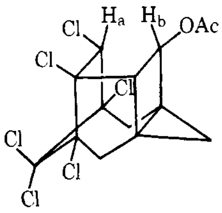
(13) N. Bloembergen, E. M. Purcell, and R. V. Pound, *Phys. Rev.*, **73**, 679 (1948).

(14) A. Abragam, "The Principles of Nuclear Magnetism," Oxford University Press, New York, N. Y., 1961, Chapter 8.

(15) J. K. Saunders and R. A. Bell, *Can. J. Chem.*, **48**, 512 (1970).

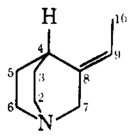
(16) R. A. Bell and J. K. Saunders, *ibid.*, **46**, 3421 (1968).

proton. However, saturation of the H(1) signal had no significant effect on the signals due to either methyl group, indicating that methyl protons relax each other and that outside protons have little effect. A very strong nOe is observed for the half-cage acetate (II) between H_a and H_b which are in close proximity. In this case, even dissolved oxygen had little effect on the observed signal intensity enhancements.

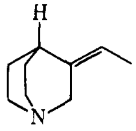


II

Nouls, van Binst, and Martin[17] applied the intramolecular nOe to a study of the geometry of two isomeric 3-ethylidene-1-azabicyclo[2.2.2]octanes (III and IV). In one isomer the C_9–C_{10} bond is cis while in the other it is trans with respect to the C_4–H bond. In III C_9–Me lies close to C_4–H, while in IV it lies a greater distance away. Thus in III, C_9–Me should contribute appreciably to the relaxation of C_4–H, while this effect should be negligible in IV. This is confirmed by nOe experiments.

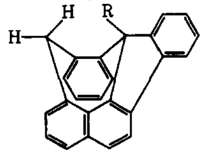


III

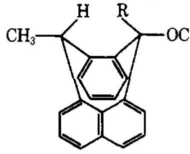


IV

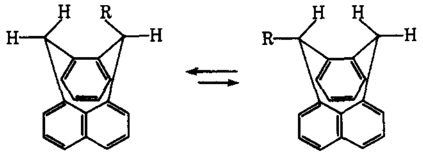
The application of the intramolecular nuclear Overhauser effect to stereochemical problems was described by Colson, Lansbury, and Saeva[18] who investigated 12-R-1,12-(*o*-phenylene)-7,12-dihydropleiadenes (V, VI, and VII). In V, conformational inversion is impossible, and on irradiation of the methyl signal, a 27% signal increase is observed for the C-7 proton signal relative to the equatorial C-7 proton signal. The methoxy compound (VI) undergoes ring inversion but exists in the diequatorial conformation as shown. This is consistent with the observation of nOe's between the transannular axial methine protons. Compound VII exists as a 2:1 mixture of axial and equatorial conformers at −20°. Irradiation of the axial C-12 proton when C-7 methoxy is equatorial results in a nOe at the axial C-7 proton. However, irradiation of the axial C-12 proton in the other conformer has no effect, due to the C-7 proton being equatorial. These results establish transannular nOe's between C-7 and C-12 axial groupings. Thus the authors used nOe's to make several structural assignments which could be made only tenuously using conventional techniques.



V, R = CH_3

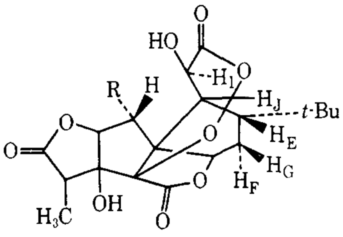


VI, R = H



VII, R = OCH_3

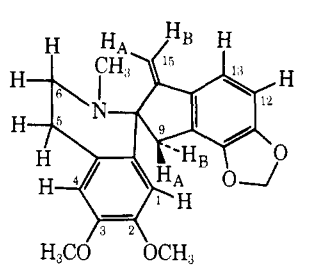
A further example of the use of nOe's in structural elucidation has been described by Woods, *et al.*,[19] in their study of the "ginkgolides" isolated from *Ginkgo biloba.* The basic structure had been determined by conventional means to be VIII. An nOe is observed between the *tert*-butyl group and the protons H_I, H_J, H_E, and H_F. This is observed even on dissolving the compound in trifluoroacetic acid, indicating that the *tert*-butyl group tends to insulate the protons from the solvent molecules. Also, the nOe indicates that the *tert*-butyl group must be close to the above protons, suggesting the quasi-equatorial position of the *tert*-butyl group.



VIII

Lippmaa, Alla, and Sugis[20] have studied a series of *tert*-butyl substituted aromatic compounds such as 4-*tert*-butylphenol, 2,4-di-*tert*-butylphenol, 2,4,6-tri-*tert*-butylphenol, 4-*tert*-butylthiophenol, 4-*tert*-butylanisole, etc., and have observed intramolecular nOe's in the ring protons in all cases when saturating the protons of the *tert*-butyl group. They are able to detect hindered rotation of the *tert*-butyl group in 2- and 6-substituted derivatives. The magnitude of the effects observed in dilute solution does not decrease when using solvents containing H or F, but does decrease with increasing distance of the proton from the irradiated group. When solutions were concentrated, intramolecular as well as intermolecular effect were observed.

Bell and Saunders[16] have studied intramolecular nuclear Overhauser effects in the alkaloid ochotensimine (IX) and have reported the first example of negative as well as positive nOe's in an all-proton system, as well as the first nOe between geminal protons. On saturating H_A-15, the signal area for H_B-15 increases by 40% while that for H-13 decreases by 8%. Similarly, on saturating H_B-15, the area for H-13 increases by 24% while that for H-12 decreases by 7%. The authors attribute this behavior to the fact that protons H_A-15, H_B-15,



IX

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[17] J. C. Nouls, G. van Binst, and R. H. Martin, *Tetrahedron Lett.*, 4065 (1967).

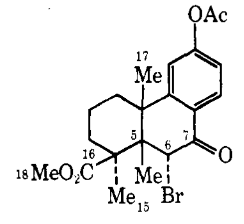
[18] J. G. Colson, P. T. Lansbury, and F. D. Saeva, *J. Amer. Chem. Soc.*, **89**, 4987 (1967).

[19] M. C. Woods, I. Miura, Y. Nakadaira, A. Terahara, M. Maruyama, and K. N. Nakanishi, *Tetrahedron Lett.*, 321 (1967).

[20] E. Lippmaa, M. Alla, and A. Sugis, *Eesti NSV Tead. Akad. Toim., Fuus., Mat.*, **16**, 385 (1967); *Chem. Abstr.*, **68**, 110042 (1968).

H-13, and H-12 are contiguous. The authors also measure a 40% nOe for the geminal protons H_A-15 and H_B-15. The magnitude of this effect is attributed to the very small scalar coupling between these protons.

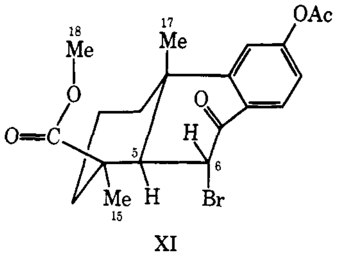
Bell and Osakwe[21] have studied the 6-bromo-7-oxo diterpenoid 12-acetoxy-6-bromo-12-methoxy-7-oxopodocarpa-8,11,13-trien-16-oate (X) and have detected nOe's which define the configuration of the bromine atom and give information on the preferred conformation of the middle ring in solution. Results obtained by the authors are collected in Table I. A number of conclusions can be drawn from these data: (a) the 6-proton is one the same side of the molecule as 17-methyl, and (b) the bromine thus has an α configuration since in the β position it would place 6-H and 17-Me at least 3.5 Å apart; (c) the 6-H is closer to 15-Me than the 17-Me; and so (d) the preferred conformation of the middle ring in solution must be the boat or twist-boat conformation. The authors suggest that protons lying close to or within each others' van der Waals radius will be able to relax each other efficiently and will show an appreciable nuclear Overhauser effect. The structure of the molecule may be written as XI.



X

Table I

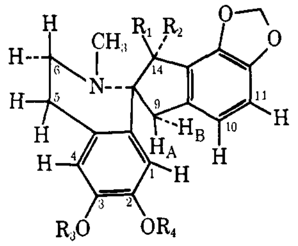
Protons satd	*% area increase of 6-H peak*	*Internucl dist, Å*
5-H	4–5	2.95
15-CH_3	21	2.6
17-CH_3	10	2.3
18-CH_3	2–3	3.0



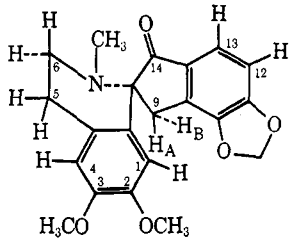
XI

The authors also caution against a failure to distinguish between a saturating field which may be quite weak and a stronger decoupling field in nOe experiments.[22]

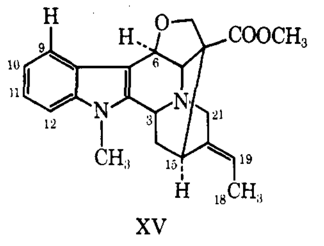
Another use of the intramolecular nuclear Overhauser effect was described by Saunders, Bell, Chen, and MacLean.[23] The authors studied the alkaloids XII and XIII, isolated by Manske.[24] They first studied the related ketone XIV. An nOe was observed for H-4 on irradiating the C-5 protons, which could not be independently saturated.[25] A 21% nOe was observed between H-4 and the methoxyl group appearing at 3.82 ppm, which defined the chemical shift of the C-3 methoxyl group. Similarly the C-2 methoxyl gave a 28% nOe for H-1. This demonstrates the use of nOe's to locate OCH_3 groups in aromatic rings. The proton at C-13 is affected by saturation of H-12 but not of the C-9 protons. However, saturation of these protons gives a 25% nOe for H-1, demonstrating the proximity of H-1 and C_9-H_A. Thus the nOe data agree with the projected structure XIV. The nOe data obtained for XII were similar to those obtained for XIV. However, a 19% nOe was observed for H-10 when the C-9 protons were saturated. The methylenedioxy function in XII is therefore at the 12,13 position. Simultaneous saturation of both *N*-methyl and C-10 protons results in an 11% nOe for the C-9 protons. An nOe is observed for H-4 on saturation of the C-5 protons and for H-1 on saturation of the C-9 protons, just as is observed for XIV. Thus, the basic structure of XII has been determined, as has its preferred conformation. For the alcohol XIII, nOe's are observed for the C-1 and C-4 protons when the methoxyl groups are saturated, indicating that they occupy the 2 and 3 positions. The protons at C-9 on saturation give an nOe for the proton at C-10, which implies that the methylenedioxy group occupies the 12,13 positions. Since the proton at C-1 shows an nOe on saturation of the C-9 protons, XIII must have a skeletal structure identical with that of XIV, with substitution as in XII.



XII, $R_1 + R_2 = O$; $R_3 + R_4 = CH_2$
XIII, $R_1 = H$; $R_2 = OH$; $R_3 = R_4 = Me$



XIV



XV

Another nOe study of an alkaloid was undertaken by Nouls and Wollast[26] who were interested in the dehydrovoachalotine XV. This molecule is suited to an nOe study owing to its rigid skeleton. In addition, in the nmr spectrum of the alkaloid, every alicyclic proton peak can be assigned by first-order analysis.[27] The authors used nOe experiments to assign the low-field aromatic multiplet to H-9 and to confirm the geometry of the ethylidene side chain. On saturation of H-6 the low-

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(21) R. A. Bell and E. N. Osakwe, *Chem. Commun.*, 1093 (1968).

(22) J. D. Baldeschwieler and E. W. Randall, *Chem. Rev.*, **63**, 81 (1963).

(23) J. K. Saunders, R. A. Bell, C. Y. Chen, and D. B. MacLean, *Can. J. Chem.*, **46**, 2876 (1968).

(24) R. H. Manske, *Can. J. Res.*, **16B**, 438 (1938).

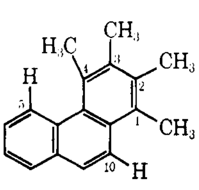
(25) B. M. Fung, *J. Amer. Chem. Soc.*, **90**, 219 (1968).

(26) J. C. Nouls and P. Wollast, *Tetrahedron Lett.*, 2731 (1968).

(27) G. Tirions and M. Kaisin, *Chimia*, **22**, 87 (1968).

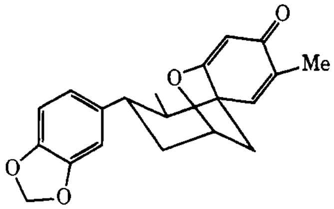
field aromatic multiplet underwent a 25% enhancement while the rest of the aromatic region was unchanged, indicating that H-9 was the deshielded aromatic proton. On saturation of H-9, no nOe was observed for H-6. CH$_3$-18 was proved to be cis to H-15 by irradiating the CH$_3$-18 signal, whereupon the signal of H-15 increased by 26%.

Martin and Nouls[28] reported the study of intramolecular nuclear Overhauser effects in the 1,2,3,4-tetramethylphenanthrene molecule XVI. On saturation of the 4-CH$_3$ signal, the 5-H signal increased in intensity by 33%. However, saturation of either 3-CH$_3$ or 2-CH$_3$ had no effect on the aromatic protons. When 1-CH$_3$ was irradiated, the integrated area of the H-10 proton increased by 11%. The authors were able to assign all the methyl signals observed for the molecule using the nOe technique and suggested that nOe experiments "can give valuable information in the field of overcrowded aromatic hydrocarbons."

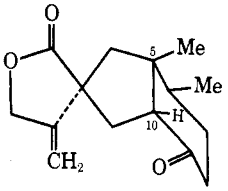


XVI

Woods and Miura[29] used the intramolecular nuclear Overhauser effect to assign the signals observed in the spectrum of the natural product futoenone (XVII) and related compounds and to confirm structures deduced from physical and chemical investigations. In a similar vein Abe and coworkers[30] studied the compound XVIII isolated from the bud of *Petasites japonicus*. They found an nOe due to 10-H on irradiation of 5-Me, thus establishing that 10-H and 5-Me are on the same side of the ring. Using this and other nmr data, in particular a study of coupling constants, the authors proposed structure XVIII.

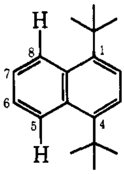


XVII



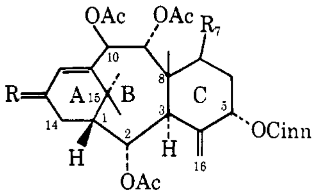
XVIII

Franck and Yanagi[31] observed an nOe on saturating the *tert*-butyl groups in 1,4-di-*tert*-butylnaphthalene (XIX), whereupon the signals due to protons at C-5 and C-8 increased in intensity by 15%.



XIX

An application of the intramolecular nuclear Overhauser effect to defining the relative stereochemistry and conformation of taxane derivatives has been reported.[32] At least five asymmetric centers in taxinine (XX) can be determined as to relative configuration (relative to C$_1$) by the use of nOe's, as well as allowing an unambiguous assignment of the C-15 methyl signals. When 15-β-Me is irradiated, the areas due to C-2 and C-9 protons increase by 10–20%. A similar effect is noted for C-21 and C-10 protons on irradiation of 12-Me. The only structure for taxinine which can account for these nOe's is XXIV. An nOe study of XXI, XXII, and XXIII led to the establishment of structure XXV; nOe's were observed as indicated by the arrows in XXIV and XXV. The similarity of the spectra of XXI, XXII, and XXIII to that of taxinine (XX) led to the proposal of planar structures. Similar nOe's

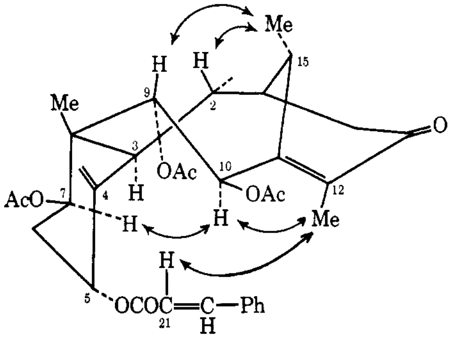


XX, R = O; R$_7$ = H

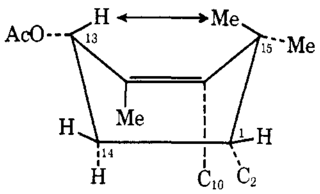
XXI, R = O; R$_7$ = OAc

XXII, R = $<^{H}_{OAc}$; R$_7$ = H

XXIII, R = $<^{H}_{OAc}$; R$_7$ = OAc



XXIV



XXV

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(28) R. H. Martin and J. C. Nouls, *Tetrahedron Lett.*, 2727 (1968).

(29) M. C. Woods and I. Miura, *ibid.*, 2009 (1968).

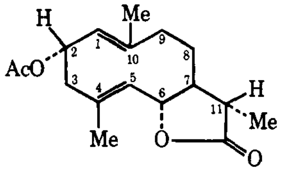
(30) N. Abe, R. Onoda, K. Ro, and T. Kurihara, *ibid.*, 1993 (1968).

(31) R. W. Franck and K. Yanagi, *J. Org. Chem.*, **33**, 811 (1968).

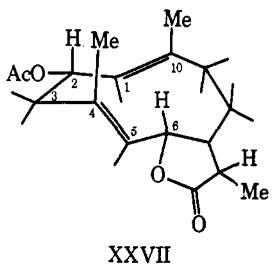
(32) M. C. Woods, H.-C. Chiang, Y. Nakadaira, and K. Nakanishi, *J. Amer. Chem. Soc.*, **90**, 522 (1968).

were observed for ring C. In XXIII, the relative configurations of eight asymmetric centers have been determined from nOe's, that is C_2, C_3, C_7, C_8, C_9, C_{10}, and C_{13}, with respect to the configuration of C_1.

Bhacca and Fischer[33] have used the intramolecular nuclear Overhauser effect to determine the configuration of dihydrotamaulipin-A acetate (XXVI). These *trans,trans*-cyclodeca-1,5-dienes show anomalous uv spectra due to transannular conjugation of the double bonds across the ring. Molecular models imply that the double-bond planes must be approximately perpendicular to the ring plane. The double bonds may have either a parallel or crossed spatial arrangement. Thus the molecule in question can have four different conformations, since it is substituted at C-4 and C-10. Although early studies[34] indicate a parallel double-bond orientation, the stereochemical course of such reactions as the Cope rearrangement and transannular additions suggest a crossed orientation. The nmr spectrum of XXVI was studied in C_6D_6. When 4-Me was irradiated, the C-6 lactonic proton signal increased by 15% as did the 2-H signal (10%). Irradiation of 10-Me resulted in a 15% increase in the 2-H proton signal. No interactions between 4-Me and the C-1 olefinic proton were detected. The conclusion is therefore that the 4-Me group is directed in space like the C-6 lactonic proton and the C-2 proton which are both β-oriented.[35] Since the 4-Me and 10-Me groups interact with the β-oriented proton at C-2, the Me groups must have a syn orientation. The planes of the double bonds are thus approximately perpendicular to the plane of the medium ring with a crossed orientation of double bonds. The 4-Me and 10-Me groups are on the same side of the plane of the medium ring. Thus the molecular geometry is depicted by XXVII.

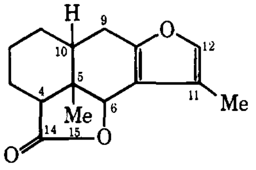


XXVI

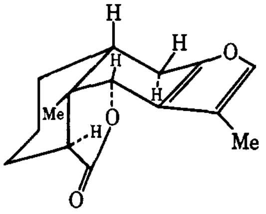


XXVII

Ishizaki, Tanahashi, Takahashi, and Tori[36] have used intramolecular nuclear Overhauser effects to determine the structure of furanoeremophilae 14β,6α-oxide (XXVIII). The existence of an nOe between 6-H and the *tert*-methyl group implies the situation of that group at C-5 and an arrangement cis to 6-H. Another nOe is observed between 6-H and the β-methyl group on the furan ring suggesting that C-6 is attached to the other β position of the furan ring. This information, along with chemical evidence and other nmr data, was used to determine the stereostructure XXIX.

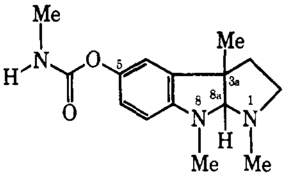


XXVIII



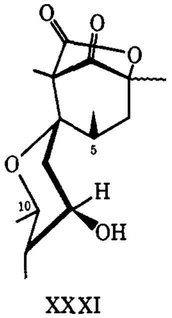
XXIX

Newkome and Bhacca[37] studied nOe's associated with the physostigmine molecule (XXX) in order to assign the ring fusion between the fused pyrrole rings, to determine the absolute configuration of the asymmetric center at 8a, and to assign the configuration of the *N*-methyl groups. The experiments were done in 10% $CDCl_3$ solutions. When the 3a-methyl signal was irradiated at low intensity, a 15% enhancement in the 8a-H signal was noted. A similar intensity increase was observed on irradiating the 8-N-Me signal. No increase was found on irradiating the 1-N-Me signal. The authors have concluded that the fused five-membered rings are cis and that 8-N-Me is cis to 8a-H, and are not undergoing rapid nitrogen inversion. The 1-N-Me stereochemical relationship to 8a-H must be completely trans or must be rapidly undergoing inversion.



XXX

A similar use of the nuclear Overhauser effect in configuration determination has been reported by Aberhart and Overton[38] who studied portentol (XXXI) and detected a 30% nOe between H-10 and C-5 Me.



XXXI

Using conventional chemical and spectroscopic techniques, Tomimatsu and Hashimoto[39] proposed the partial structure XXXII for poncitrin, a coumarin isolated from the root of *Poncirus trifoliata*. The signals due to the two *gem*-dimethyl groups and the methoxy group were successively saturated by double irradiation. The results led to the proposal of structure XXXIII as the correct structure, since signals due

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[33] N. S. Bhacca and N. H. Fischer, *Chem. Commun.*, 68 (1968).

[34] F. Sorm, *Progr. Chem. Org. Natur. Prod.*, 19, 1 (1961).

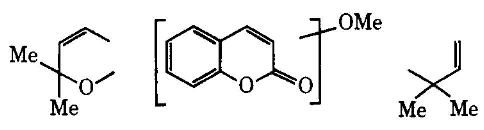
[35] N. H. Fischer, T. J. Mabry, and H. B. Kagan, *Tetrahedron*, 24, 4091 (1968).

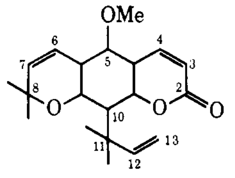
[36] Y. Ishizaki, Y. Tanahashi, T. Takahashi, and K. Tori, *Chem. Commun.*, 551 (1969).

[37] G. R. Newkome and N. S. Bhacca, *ibid.*, 385 (1969).

[38] D. J. Aberhart and K. H. Overton, *ibid.*, 162 (1969).

[39] T. Tomimatsu and M. Hashimoto, *ibid.*, 168 (1969).

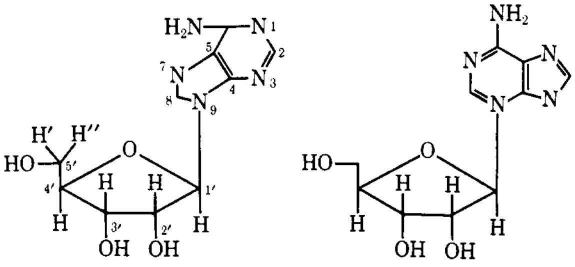

XXXII



XXXIII

to H-4 and H-6 both increased on irradiating the OCH_3 signal. The presence of the 2,2-dimethylchromene and 1,1-dimethylallyl groups was also confirmed by nOe studies, and their *gem*-dimethyl groups were assigned using that technique.

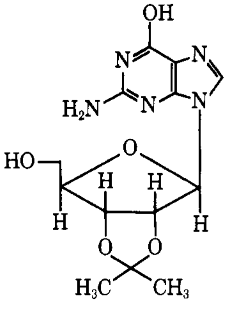
Hart and Davis[40] applied the nuclear Overhauser effect to the study of biochemical molecules, in particular the conformation of polynucleotides in the purine riboside series XXXIV. Previous to the development of nOe techniques the

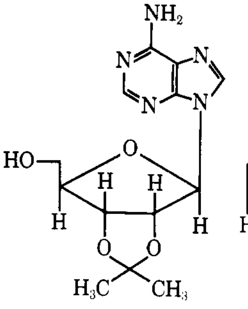


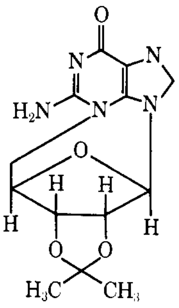
anti syn

XXXIV

conformational analysis of the glycosidic bond in the purine riboside series had been a difficult problem, since rotation about that bond was apparently quite facile. H-8 should be useful in nOe experiments since in the anti conformation H-8 and H-1′ are 3.4 Å apart, while in the syn conformation they are 1.8 Å apart. In addition, H-8 is closer to H-2′, H-3′, H-5′, and H-5′′ in the syn conformation than in the anti conformation. Molecules XXXV, XXXVI, and XXXVII were


XXXV


XXXVI

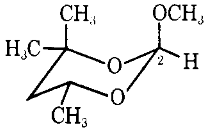

XXXVII

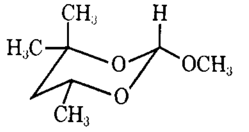
examined for nOe's. The results are presented in Table II. Thus in XXXVII, H-8 only interacts with H-1′ and not with H-2′ or H-3′. However, in XXXV, H-8 interacts with H-1′, H-2′, H-5′, and/or H-5′′, and in XXXVI, H-8 and H′ interact. It thus appears that both syn-like and anti-like conformations are possible for both adenosine and guanosine nucleosides under the experimental conditions, but that quantitative differences exist.

Table II

Molecule	*Proton irradiated*	*Proton observed*	*% enhancement*
XXXV	H-8	H-1′	20
	H-1′	H-8	12
	H-2′	H-8	12
	H-5, H-5′′	H-8	10
	H-4′	H-8	2
XXXVI	H-1′	H-8	23
	H-2′	H-8	9
	H-3′	H-8	3
	H-5′, H-5′′	H-8	4
	H-1′	H-2	0
XXXVII	H-8	H-1′	26
	H-1′	H-8	39
	H-2′, H-3′	H-8	1

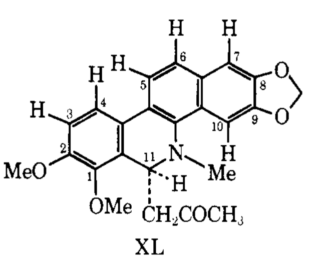
Eliel and Nader[41] in their investigation of the stereochemistry of the reaction of Grignard reagents with ortho esters have used the intramolecular nuclear Overhauser effect to assign the configuration of the cis and trans methoxydioxanes XXXVIII and XXXIX. In the compound assigned


XXXVIII (trans)


XXXIX (cis)

the cis configuration by dipole data and chemical shift experiments, saturation of one of the two singlet methyl groups results in a 12% enhancement of the signal due to H-2. This effect is not observed for the compound assigned the trans configuration. Thus H-2 and Me are in close proximity in the cis compound but not in the trans analog.

The nuclear Overhauser effect was used by MacLean, *et al.*,[42] to assign the nmr signals observed for the alkaloid dihydrochelerythrine (XL). An nOe was observed between



XL

the N-Me signal and the signal at δ 7.50 which enabled that signal to be attributed to H-10. An nOe of 24% was observed at δ 6.94 on irradiation of the OCH_3 signals. This signal was therefore attributed to H-3. Similar experiments enabled all signals to be assigned to individual protons or groups of protons.

Bell and Saunders used the intramolecular nuclear Overhauser effect to measure internuclear distances in organic molecules.[8] They studied a series of compounds and plotted

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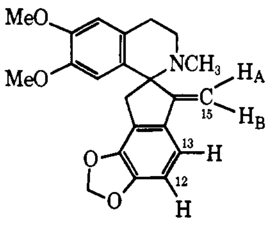
[40] P. A. Hart and J. P. Davis, *J. Amer. Chem. Soc.*, **91**, 512 (1969).

[41] E. L. Eliel and F. Nader, *ibid.*, **91**, 536 (1969).

[42] D. B. MacLean, D. E. Gracey, and J. K. Saunders, *Can. J. Chem.*, **47**, 1951 (1969).

observed nOe's *vs.* internuclear distance as determined from Dreiding models.[43] Using logarithmic axes they found a straight-line relationship between the reciprocal of the nOe and the sixth power of the internuclear distance, with slope -6, both when irradiating and observing protons, and when irradiating Me groups and observing protons. This is in accordance with eq 5. The excellent linearity of the plots exemplifies the predominance of the dipole–dipole relaxation mechanism and the predominance of intramolecular interactions over intermolecular effects. The authors determined the value of constant A in eq 5 to be 1.8×10^{-2} for H–H and 0.98×10^{-2} for Me–H interactions. Thus, by observing nOe's in a molecule of unknown structure, it may be possible, by employing eq 5, to estimate the internuclear distance between protons and between protons and methyl groups. Should a single proton be relaxed by a group of nonequivalent protons, only the ratio of internuclear distances could be determined. A technique was also described for determining whether a given proton is relaxing through more than one other proton, based on the nonequivalence of T_{AA} and T_{BB} (see eq 4). For example, in ochotensimine (XLI) irradiation of C_{13}-H gives an nOe of 8% at C_{15}-H_B, but irradiation of C_{15}-H_B gives a 24% nOe at C_{13}-H. Thus both C_{13}-H and H_B have different protons involved in their relaxation processes.



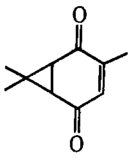
XLI

Still, Macdonald, and Oh[44] used the intramolecular nuclear Overhauser effect to study the products of the photochemical addition reactions of 3-carene-2,5-dione (XLII). The two main products are referred to as XLIIIa, XLIIIb, and XLIV. For dimer XLIV, the nOe results are as shown in Table III.

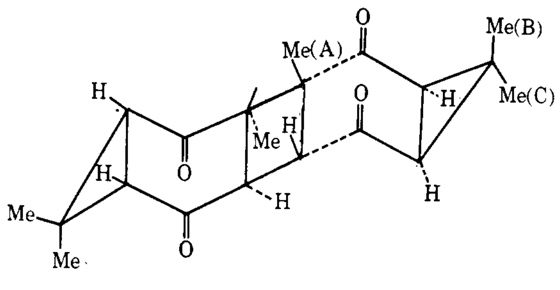
Table III

Obsd protons	*δ (ppm)*[a]	*Irrad protons*	*δ (ppm)*[a]	*% area increase*	*Internucl dist, Å*
Cyclobutyl	2.91	Me(A)	1.49	24	2.2
Cyclobutyl	2.91	Me(B)	1.28	0	5.5
Cyclobutyl	2.91	Me(C)	1.11	0	2.8
Cyclopropyl	2.19	Me(A)	1.49	0	2.9
Cyclopropyl	2.19	Me(B)	1.28	18	2.3
Cyclopropyl	2.19	Me(C)	1.11	0	3.6

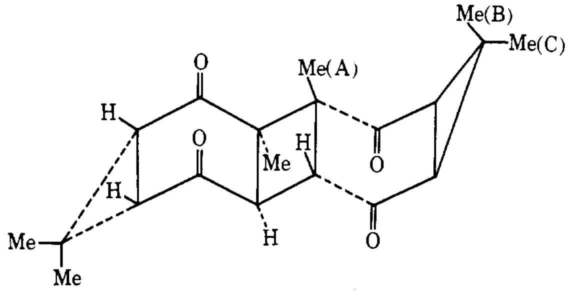
[a] Relative to TMS internal standard.



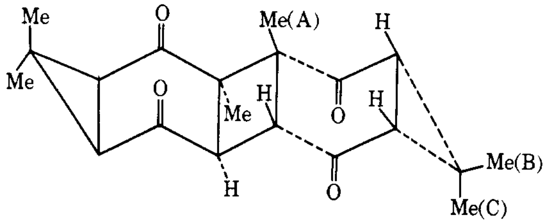
XLII



XLIIIa



XLIIIb



XLIV

Table IV

Obsd protons	*δ (ppm)*	*Irrad protons*	*δ (ppm)*	*% area increase*	*Internucl dist, Å a*	*b*
Cyclobutyl	3.03		1.45	6		
Cyclobutyl	3.03		1.40	20		
Cyclobutyl	3.03	Me(A)	1.37	28	2.2	2.2
Cyclobutyl	3.03	Me(B)	1.33	32	3.6	0.9
Cyclobutyl	3.03	Me(C)	1.30	11	4.7	4.3
Cyclobutyl	3.03		1.25	5		
Cyclopropyl	2.39		1.45	2		
Cyclopropyl	2.39		1.40	6		
Cyclopropyl	2.39	Me(A)	1.37	8	1.1	3.7
Cyclopropyl	2.39	Me(B)	1.33	14	3.6	3.6
Cyclopropyl	2.39	Me(C)	1.30	20	2.3	2.3
Cyclopropyl	2.39		1.25	10		

In compound XLIV the methyl resonances found at δ 1.49, 1.28, and 1.11 are due to the cyclobutyl, cisoid cyclopropyl methyl, and transoid cyclopropyl methyl resonances, respectively, since the nOe is a function of internuclear distance. Apparently, there are no intramolecular effects between the cyclobutyl methine protons and the transoid cyclopropyl methyls. The data for XLIII are given in Table IV. For XLIII, the resonance at δ 1.30 ppm is due to the cisoid cyclopropyl methyls. Apparently there are no relaxation effects on the cyclopropyl ring protons due to the other methyl protons. The cyclobutyl ring protons are relaxed by methyl groups at

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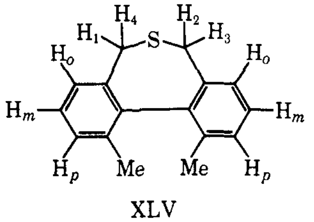
(43) A. Dreiding, *Helv. Chim. Acta*, **42**, 1339 (1959).

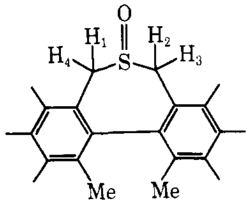
(44) I. W. Still, C. J. Macdonald, and Y.-N. Oh, *Can. J. Chem.*, **48**, 1526 (1970).

δ 1.33 and 1.37 ppm. Molecular models imply the only structure for XLIV to be the one shown, due to steric effects. However, XLIII can have two conformers, a and b. In Table IV the two instances where internuclear distances vary considerably between the two conformers, when considered with the observed nOe, suggest a preference for the b conformer.

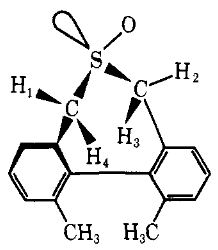
Fraser and Schuber[45] have used the intramolecular nuclear Overhauser effect to determine the configuration of the benzylic protons responsible for each absorption in the nmr spectrum of 1,11-dimethyl-5,7-dihydrodibenz[*c*,*e*]thiepin (XLV), its *S*-oxide, and its *S*-dioxide. In each of these compounds, one of each pair of diastereotopic protons (the one with configuration "pro-S") lies closer to the ortho aromatic proton than the other. Thus, on irradiating this proton, the diastereotopic proton giving the larger nOe must have the pro-S configuration. To isolate the ortho protons, the meta protons were replaced by deuterium atoms. On irradiating the ortho proton signal, a larger nOe is observed between H_o and H_1 than between H_o and H_2, and the conclusion is drawn that H_1 is closer to H_o and has the pro-S configuration. A negative nOe is observed for H_2 on irradiation of H_o and is explainable as discussed previously. The nOe for H_1 on irradiating H_o is smaller than that observed for H_o on irradiation of H_1. This indicates a dominating relaxation between H_1 and H_2. The observation of these nOe's involved the use of "triple irradiation" in which an oscillator was tuned to each line of the doublet for H_1 or H_2. The sulfoxide XLVI has four nonequivalent benzylic protons, two nonequivalent methyls, and six nonequivalent aromatic protons, since the sulfoxide group is pseudoasymmetric. The configurational assignments of all four benzylic protons is possible from the nOe data. When H_m = D, no nOe was observed between H_1 or H_4 and the ortho aromatic protons when using $CDCl_3$ as solvent. Replacing H_1 or H_4 by D had no effect in producing a nOe. However, using DMSO-d_6 as solvent allowed the observation of nOe's in the usual way. This was attributed to the tendency of sulfoxides to dimerize. The stereostructure of the sulfoxide was determined to be XLVII.



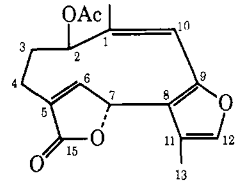
XLV



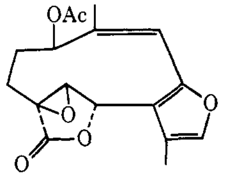
XLVI



XLVII

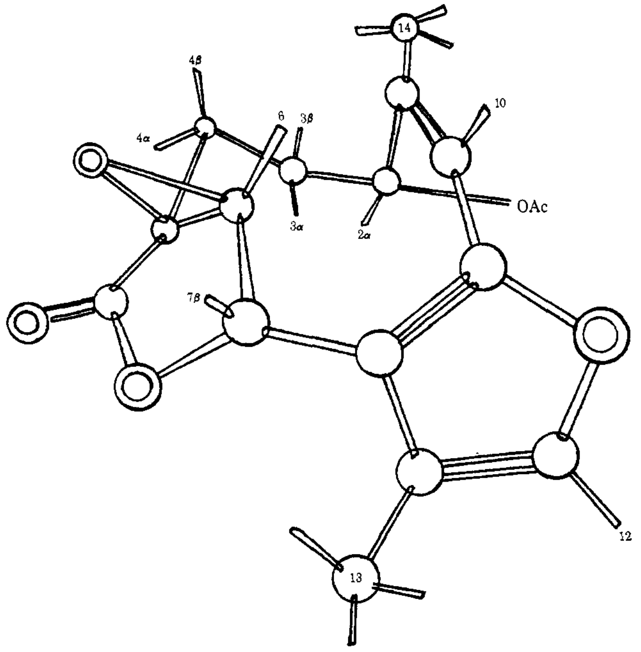


XLVIII



XLIX

The use of nOe's in determining the conformations of ten-membered carbocyclic rings has been demonstrated by Tori, *et al.*,[46] who studied zeylanine I and zyelanine II (XLVIII and XLIX). Dreiding models suggest that two conformations of the molecules exist. In one, H-6 and Me-1 are syn, and in the other they are both anti. In both compounds, irradiation of the H-10 signal causes an increase in the integrated intensity of the H-6 signal, indicating that the ten-membered rings adopt conformations in which H-6 and Me-1 are syn. The larger nOe observed for XLIX indicates that H-6 and H-10 are closer to each other than in XLVIII. Complete saturation of Me-1 in XLIX does not cause an increase in the integrated area of H-6. Another considerable nOe is observed between H-7β and Me-11 in XLIX, suggesting the molecular conformation of that molecule to be as pictured in L. The situation for molecule XLVIII is similar to that for XLIX.



L

In a very pretty experiment[47] the conformational preferences of 4-bromo-2-furaldehyde, 4-bromo-2-thiophenecarboxaldehyde, and 2-acetyl-4,5-dibromothiophene were investigated.

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[45] R. R. Fraser and F. J. Schuber, *Can. J. Chem.*, **48**, 633 (1970).

[46] K. Tori, M. Ohtsuru, I. Horibe, and K. Takeda, *Chem. Commun.*, 943 (1968).

[47] S. Combrisson, B. Roques, P. Rigny, and J. J. Basselier, *Can. J. Chem.*, **49**, 904 (1971).

The thiophene derivatives exist as the OS-cis isomers at room temperature. The furan derivative exists in an equilibrium between OO-cis and OO-trans forms at −99°, the former being preferred. The equations for the nOe effect can be modified to take into account the effective intramolecular chemical exchange due to rotation of the carbonyl group at higher temperatures,[47] and rough estimates of conformational lifetimes are possible.

Acknowledgments. We are grateful to two referees for their very helpful criticism and to the National Research Council of Canada for financial assistance.