Proton Spin-lattice Relaxation Studies. *N*-Aryl-1-isoindolinones

*Mohammad A. Khadim and Lawrence D. Colebrook**

Department of Chemistry, Concordia University, 1455 de Maisonneuve Blvd., West, Montreal, Quebec, Canada H3G 1M8

and

Laurance D. Hall

Department of Chemistry, The University of British Columbia, Vancouver, B.C., Canada V6T 1W5

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Proton spin-lattice relaxation rates (R_1 values) have been measured, at 270 MHz, for a series of *N*-aryl isoindolinones. A normalization procedure has been used to enable comparison of R_1 values in different compounds by minimizing the effects on relaxation rates of changes in motional correlation times accompanying changes in substitution patterns. A substantial (4.3-fold) dynamic range of R_1 values has been observed, and individual values have been correlated with the molecular environments of the nuclei. There is evidence for an interring relaxation process.

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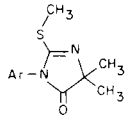
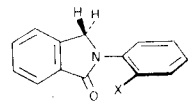
Although the measurement of proton spin-lattice relaxation rates (R_1 values) can be carried out on a routine basis using modern pulse Fourier transform spectrometers, relatively few applications to heterocyclic compounds in solution have been reported. These include studies of carbohydrate (1) and nucleoside (2) derivatives, the alkaloid vindoline (3,4) and certain other heterocyclic compounds (5). We have recently carried out an experimental evaluation of simplified procedures for determining the proton spin-lattice relaxation rates of natural products, including alkaloids as examples (4), and have reported (6) relaxation studies on a series of 1-aryl-4,4-dimethyl-2-methylthio-2-imidazolin-5-ones (I).



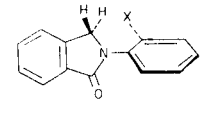
I

As part of our program of investigating the potential of proton R_1 values for the determination of molecular structure and conformation we now report proton relaxation studies of a second series of synthetic aryl-substituted nitrogen-containing compounds, namely, *N*-aryl-1-isoindolinones (Table 1). These compounds were prepared for our studies (7) on aryl substituted nitrogen heterocycles which may exhibit biphenyl-like isomerism. Details of their ^1H and ^{13}C spectra will be published elsewhere.

Although these compounds (with the exception of **1** and **9**) may exist as enantiomeric rotational isomers (II and III), so that the 3-methylene protons are diastereotopic, no evidence for slow internal rotation about the aryl C-N bond can be detected. The 3-methylene proton signals, which would take the form of AB quartets if rotation were slow on the nmr time scale and if the chemical shift differences were adequate, remain as sharp singlets at low



II



III

temperatures (about −150°, 100 MHz spectra). Thus it may be assumed that internal rotation about the aryl C-N bond is fast under the experimental conditions used for the R_1 measurements in the present study.

If a molecule is tumbling rapidly in solution, so that the extreme narrowing condition ($\omega_0^2\tau_c^2 \ll 1$) is met, the relaxation rate of a nucleus will normally be dominated by the intramolecular dipole-dipole mechanism. This shows the following dependence on molecular parameters:

$$R_1^R = 1/T_1^R \propto \frac{\gamma_D^2 \cdot \gamma_R^2}{(r_{D,R})^6} \cdot \tau_c(D,R)$$

D and R refer to the donor and the receptor nuclei, respectively, the γ's are the magnetogyric ratios, r is the internuclear distance, and τ_c is the motional correlation time for the D,R vector. The usefulness of R_1 values for providing information on molecular structure and conformation is principally due to the very strong (inverse sixth power) dependence on the internuclear distance. Because the ability of one nucleus to relax another is attenuated very rapidly with increasing internuclear distance, the relaxation rate of a particular nucleus will be largely dependent on the number and location of its near neighbors with large magnetogyric ratios. Since in most compounds, only protons will have large enough magnetogyric ratios to be effective in proton relaxation, it follows that a proton relaxation experiment will basically provide information dependent on the location of other protons in the molecule.

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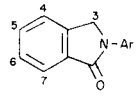
Table 1

Proton Spin-lattice Relaxation Rates (R_1 values, sec^{-1}) for *N*-Aryl-1-isoindolinones (a)



Compound	Ar	Isoindolinone protons				Aryl protons							
		3	4	6	7	3′	4′	5′	6′	2′,6′-Me	3′-Me	2′-OMe	4′-OMe
1	Phenyl	0.78	(0.34	0.38)	0.26	(0.38			0.34)				
2	2′-Tolyl	0.85	(0.38	0.41)	0.28	(0.41			0.38)	0.56			
3	2′-Methoxyphenyl	0.88	(0.41	0.46)	0.28	0.46	(0.41		0.37)			0.78	
4	2′-Fluorophenyl	0.74	(0.34	0.38)	0.28	(0.41			0.31)				
5	2′-Chlorophenyl	0.78	(0.34	0.41)	0.28	(0.41			0.36)				
6	2′-Bromophenyl	0.82	(0.29	0.38)	0.29	(0.38			0.29)				
7	2′-Hydroxyphenyl	0.90			0.28	0.43	(0.34		0.31)				
8	2′,3′-Dimethylphenyl	0.99	(0.43	0.46)	0.31		(0.43		0.38)	0.64	0.75 [0.79]		
9	2′,6′-Dimethylphenyl	0.99	(0.42	0.46)	0.31 [0.36]	0.39	0.43	0.39		0.62 [0.69]			
10	4′-Methoxy-2′-methylphenyl	1.11	(0.44	0.48)	0.32 [0.35]	0.45		0.49	0.44 [0.48]	0.71 [0.78]			0.75 [0.79]
11	3′-Chloro-2-methylphenyl	0.96	(0.41	0.46)	0.31		0.42	0.46	0.31	0.56			
12	4′-Chloro-2-methylphenyl	0.96	(0.41	0.46)	0.31	0.30		0.41	0.39	0.64			
13	1′-Naphthyl	1.04			0.31								
14	2′-Naphthyl	1.11			0.30								

(a) R_1 values were measured by the null point method with a precision of 5% or better. Numbers enclosed in [ ] are R_1 values measured by the non-linear regresssion method (initial slope conditions) from peak intensities. Values enclosed in ( ) are ranges; invididual chemical shifts are not identified.

If a molecule is not approximately spherical, it may tumble anisotropically in solution, *i.e.*, a particular axis of rotation will be preferred. Since the relaxation rate is dependent on the angle between the relaxation vector (D,R) and the preferred axis of rotation, R_1 measurements may provide information on anisotropic motion of the molecule as a whole, or of segmental motion within the molecule. In view of the shape of the molecules in the present study, and of their expected internal rotation, it was considered that anisotropic motion was likely to be a factor influencing the relaxation rates.

The dominance of the intramolecular dipole-dipole relaxation mechanism may be assured if dilute solutions in solvents which do not themselves provide relaxation pathways are employed. It is sufficient to use per-deuterated solvents for proton relaxation measurements, since the small magnetogyric ratio of deuterium makes this nucleus very inefficient for relaxation (*ca.* 6.3% that of an equivalent proton). Dissolved oxygen in the solution is usually the most important source of paramagnetic (dipole-dipole) relaxation. If required, oxygen may be removed by standard techniques, but we have shown that this is unnecessary for most qualitative studies, such as the present one (4). The rate constant for relaxation to oxygen is very similar for all protons in a molecule, so that all of the R_1 values determined for protons in a molecule will be increased by an essentially constant amount.

Since relaxation rates are dependent on rates of molecular tumbling, a change in the mass or geometry of a substituent in a molecule may affect the R_1 values of all of the nuclei, not only those in the immediate vicinity of the substitution site. Thus, if the R_1 values of molecules with different substituents or geometries are to be compared, it is advisable to normalize the relaxation rates with respect to the rate of a nucleus remote from the site of substitution, on the assumption that changes in the R_1 values of this nucleus will reflect changes in the tumbling rates rather than the direct effect of the substituent. In this study the 7-proton of the invariant isoindolinone moiety was chosen since it is remote and its R_1 value could be measured with reasonable accuracy (Table 2).

Relaxation rates of the *N*-arylisoindolinones were determined by the conventional "inversion-recovery" two pulse sequence. Following a non-selective 180° perturbing pulse, which inverts the magnetization of the nuclei, and a variable delay time, t, which permits the nuclei to relax towards their equilibrium state, a 90° pulse is applied to sample the remaining magnetization. As t increases, the signals pass from their initially inverted state, through zero (the null point), then gradually recover their normal,

Table 2

Normalized Proton Spin-lattice Relaxation Rates, Relative to 7-Proton, for *N*-Aryl-1-isoindolinones (a)

Compound	Isoindolinone proton				Aryl protons							
	3	4	6	7	3′	4′	5′	6′	2′,6′-Me	3′-Me	2′-OMe	4′-OMe
1	3.00	(1.31	1.46)	1.00	(1.31			1.46)				
2	3.03	(1.36	1.46)	1.00	(1.36			1.46)	2.00			
3	3.14	(1.46	1.64)	1.00	1.64	(1.32		1.46)			2.78	
4	2.64	(1.21	1.36)	1.00	(1.11			1.46)				
5	2.78	(1.21	1.46)	1.00	(1.28			1.46)				
6	2.83	(1.00	1.31)	1.00	(1.00			1.31)				
7	3.21			1.00	1.53	(1.11		1.21)				
8	3.19	(1.39	1.48)	1.00	—	(1.22		1.39)	2.06	2.42		
9	3.19	(1.35	1.48)	1.00	1.26	1.39	1.26	—	2.00			
10	3.47	(1.38	(1.50)	1.00	1.41	—	1.53	1.37	2.22			2.34
11	3.10	(1.32	1.48)	1.00	—	1.35	1.48	1.00	1.81			
12	3.10	(1.32	1.48)	1.00	0.97	—	1.32	1.26	2.06			
13	3.35			1.00								
14	3.70			1.00								

(a) Values enclosed in parentheses are ranges, individual chemical shifts are not identified.

"upright" intensity (attained at about 5 T_1). The spectra obtained as a function of t may be displayed in the form of a stack plot (Figure 1). The relaxation rates of the individual nuclei may be obtained by fitting the theoretical expression for the exponential recovery of magnetization to the measured signal intensities as a function of "t". Intensities may be obtained by the system computer or by direct measurement from recorded spectra. The fitting process may be carried out using linear regression or graphically by a semi-log method, or by non-linear regression. However, at some possible cost in accuracy, but with a considerable saving in time (at least a factor of ten) and convenience, the R_1 values may be estimated by identifying the null points on the stack plots. At the null point, $R_1 = 0.69/t$. In comparisons of R_1 values determined by the null point and by the regression methods, we have previously (4) demonstrated that the null point method provides sufficient accuracy for qualitative studies such as the present one. The R_1 values reported in this paper were measured by the null point method, but a number of values were also determined by the non-linear regression computational method (Table 1).

EXPERIMENTAL

Spectra were determined at 270 MHz, using a "homebuilt" spectrometer, based on a Bruker WH-90 console, an Oxford Instruments superconducting magnet, and a Nicolet 1080 or 1180 computer with a 16 K word data block. Relaxation rates (at 23°C) were measured using the 180°, t, 90°, delay (inversion-recovery) pulse sequence, with averaging of four free induction decays. The delay between sequences was at least five times the estimated value of the longest T_1. Before each run, the 180° pulse length was optimized by finding the length which produced a null in the amplitude of the free induction decay. Typically, data for about thirty values of t, the maximum that could be accommodated, were averaged, filtered, Fourier transformed, phase corrected, and stored automatically on disc for later processing, the appropriate range of t values having been selected in a preliminary experiment. The longest

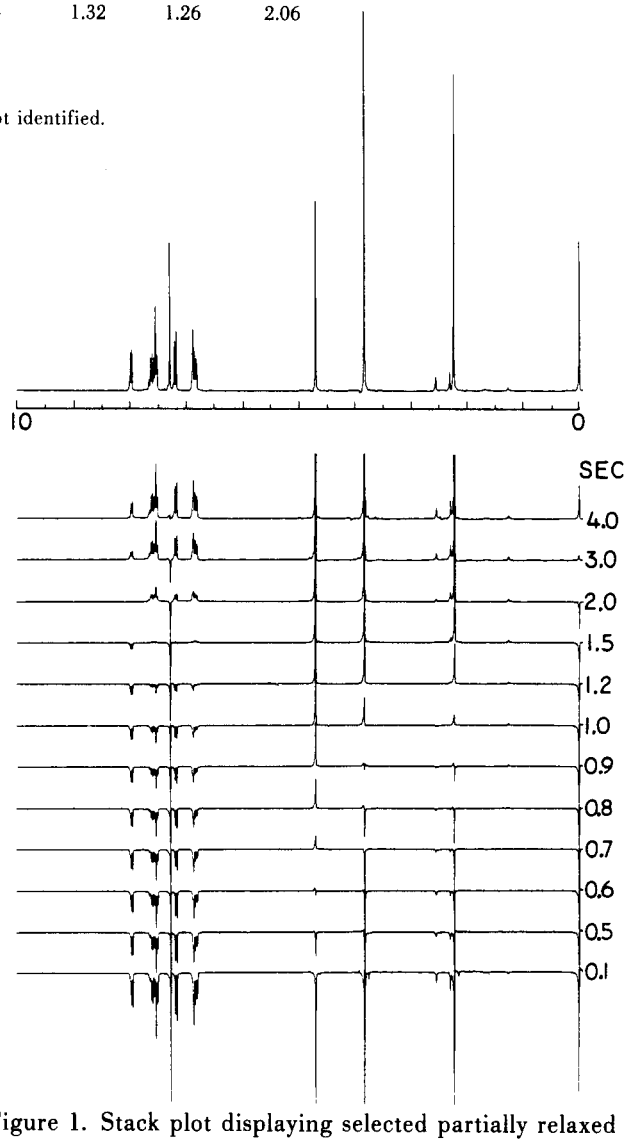


Figure 1. Stack plot displaying selected partially relaxed spectra of **10**, taken for various delay times, t, in the 180°, t, 90° pulse sequence. The delay times (t) are marked on the right hand side of the figure. The normal (fully recovered) spectrum is displayed at the top of the stack.

value of t was chosen so that all peaks had relaxed through their null point. R_1 values were determined by the "null point" method, using extrapolation between data sets straddling the null point, and also in the number of cases (Table 1) by computer fitting the peak intensities by the exponential recovery function using an iterative non-linear regression program run on a Hewlett-Packard 1000 computer. Intensities were obtained from computer print-outs. In order to avoid problems associated with non-exponential recovery of magnetization following the perturbing pulse, it is normal procedure to base the R_1 calculation on the first portion of the recovery curve (the "initial slope"). Data points out to about 1.2 T_1 were used in the present case.

Non-degassed 0.05 *M* solutions in 99.8% deuteriochloroform were used throughout, the solvent having been stored over molecular sieves.

The *N*-aryl substituted isoindole-1,3-diones were prepared by the general method described by Vogel (8). The *N*-aryl-1-isoindolinones were prepared either by a modification of the method described by Brewster and co-workers (9) or by Clemmensen reduction of the corresponding *N*-arylisoindole-1,3-diones. Satisfactory C, H, and N analyses were obtained in all cases, while the ^1H and ^{13}C nmr spectra were consistent with the expected structures.

Results and Discussion.

The relaxation rates (R_1 values) in this series of compounds range from 0.26-1.11 sec^{-1}, a dynamic range factor of 4.3. Fastest relaxing are the 3-methylene protons, slowest are the more isolated aryl protons, in particular the 7-protons of the isoindolinone group.

R_1 values determined by both the null point and the non-linear regression methods show reasonably good agreement except in the case of the fast relaxing 3-methylene protons. This is because the chosen experimental conditions did not permit sufficient measurements for these protons to be taken within the "initial slope" range to permit accurate regression analysis.

3-Methylene protons.

The relaxation rates (R_1 values) of these protons fall within the range 0.74-1.11 sec^{-1}. These rates increase roughly in parallel with increasing molecular weight, indicating their sensitivity to changes in rates of molecular tumbling. After normalization with respect to the 7-proton rate, the relative rates fall within the range 2.64-3.70. Because of their short internuclear distance and their location in a rigid portion of the molecule, the 3-methylene protons relax each other efficiently and are, in fact, the fastest relaxing nuclei in these molecules. Less efficient relaxation pathways which may also contribute to the relaxation rates are to the 4-protons of the isoindolinone moiety, and to protons attached directly or indirectly to the *ortho* positions of the *N*-aryl group. Since all of the compounds in this series have identical isoindolinone moieties, no information on the contribution of the former relaxation pathway can be obtained. Thus, external influences on the 3-proton relaxation rates must be due to relaxation to *N*-aryl substituents, modulated by the effect of changes in substituents on the overall tumbling rates of the molecules in solution, changes in anisotropic contributions to the tumbling processes, and changes in rates of segmental motion, *i.e.*, rotation or libration about the aryl C-N bond.

Apart from a direct inter-ring dipole-dipole contribution, an *ortho* aryl substituent may influence the relaxation rates of the 3-methylene protons by changing the average dihedral angle between the aryl and the heterocyclic moieties through a steric bulk effect, thereby changing inter-nuclear distances. An increase in the steric bulk of the *ortho* substituent, X, is expected to increase the dihedral angle between the rings (II and III). An associated influence on freedom for segmental motion within the molecule may affect relaxation rates through τ_c effects.

Comparison of relaxation rates between compounds in the series is best done using the normalized rates in Table 2, so as to reduce correlation time effects as much as possible. The most striking feature of the relative rates of the 3-methylene protons is the low values for the three *ortho*-halo compounds, **4-6**. In these compounds, the relaxation rates of the 3-protons are reduced by 6-12% compared with the rates of the corresponding protons of the phenyl compound, **1**. In contrast, the 3-protons of all of the other compounds, which have proton-containing substituents in the *ortho* positions, relax faster than those of the reference compound, **1**. It is evident from this that a significant inter-ring relaxation pathway exists between the 3-methylene protons and proton-containing *ortho* substituents on the aryl group. In contrast, the presence of *ortho* halo substituents, which are less effective sources of relaxation than protons, reduces the overall relaxation contribution from the aryl group.

The increase in the normalized relaxation rates of the 3-protons with increased atomic weight of the halo substituent in **4-6** is attributed to a decrease in the rates of internal rotation, or of libration, about the aryl C-N bond as the steric bulk of the substituent increases, coupled with changes in the average dihedral angles. Thus, the molecules become more rigid as the size of the *ortho* substituent increases, and the effect of segmental motion, which reduces the relaxation rates of involved nuclei, becomes less important. This effect is also noticeable in other compounds with increasingly bulky aryl groups.

N-Aryl Protons.

In most cases, the protons on the *N*-aryl group give rise to complex multiplets, so that R_1 values could not be measured for individual protons, and only the approximate range of values could be determined (Tables 1 and 2). Only in the cases of the trisubstituted aryl systems, **9-12**, could all of the aromatic proton R_1 values be measured. In certain other cases, one of the aryl proton signals was sufficiently displaced from the others that its R_1 value could be determined (10).

The relaxation rates of the *N*-aryl protons fall in the

range 0.29-0.49 sec^{-1} (Table 1), and the normalized rates in the range 0.97-1.64 (Table 2). It was not practicable to determine any rates for the two naphthyl compounds, **13** and **14**, because of the complexity of their aryl spectra. There are a number of instances in which specific intramolecular dipole-dipole relaxation of *N*-aryl protons can be clearly illustrated. For example, in the 2′-methoxyphenyl, **3**, and the 2′-hydroxyphenyl, **7**, compounds the aryl 3-protons are relaxed by the protons on the substituents, their normalized rates, 1.64 and 1.53, respectively, being near the upper limit of the range. For geometric reasons, relaxation of an aryl proton by an *ortho* methoxyl group is more effective than by an *ortho* hydroxyl group.

Enhancement of the relaxation rates due to the presence of an *ortho* methoxyl group is also seen in the case of the 4′-methoxy-2′-methylphenyl compound, **10**. Here, both the 3′- and the 5′-protons have relaxation rates (0.45 and 0.49 sec^{-1}, respectively) which are enhanced with respect to the rate (0.44 sec^{-1}) of the isolated 6′-proton. The 3′- and the 5′-protons of **10** also relax faster than the corresponding protons of the 4′-chloro-2′-methyl compound, **12**, due to the presence of the methoxyl group in **10**. Since a methoxyl group permits closer approach to an *ortho* proton than does a methyl group, it can be more effective as a source of relaxation. This point is illustrated by a comparison of the normalized aryl proton relaxation rates of the 2′-methyl and the 2′-methoxy compounds, **2** and **3**, respectively (Table 2).

If the 3′-, 4′-, and 5′-protons of the 2′,6′-dimethyl compound, **9**, formed an isolated spin system tumbling isotropically, it can be calculated from internuclear distances (obtained from Drieding models) that the 4′-proton should relax 1.93 times faster than the other two protons. In fact, this proton relaxes only 10% faster. Since these protons are approximately symmetrically disposed with respect to the most probable axis of anisotropic motion, it is unlikely that there will exist any differential effects of tumbling motions. The relatively fast relaxation of the 3′- and the 5′-protons must, therefore, be attributed to the relaxation effects of the 2′- and the 6′-methyl groups.

Methyl and Methoxy Groups.

The spin-lattice relaxation rates for the methyl substituents in the isoindolinones fall in the range 0.56-0.75 sec^{-1}. They (and the methoxy protons) relax more slowly than the 3-methylene protons, despite the greater number of near neighbors of an individual proton within the group. This differential is a consequence of the freedom of segmental motion available to the methyl and methoxy groups, which influences the observed R_1 values with the τ_C values.

Interpretation of the variations in the normalized relaxation rates of the aryl methyl groups within the series (Table 2) in terms of substituent effects is complicated by the possibility of concomitant changes in the rates of internal motion within the molecules. The most striking feature of the normalized rates is the relatively fast relaxation of one of the two methyl groups in **8**. This group relaxes 17% faster than the other methyl in the same compound, whose normalized R_1 value is consistent with the normalized R_1 values of the *ortho* methyl groups of the other compounds in the series. The chemical shift assignments in **8** were based on reported assignments for related compounds (11); on this basis it is the *meta*- methyl group in **8** which relaxes faster than the *ortho*. However, enhancement of the relaxation rate of the *meta*-methyl protons in **8** is unexpected, so the chemical shift assignments must be considered questionable.

The methoxyl groups in **3** and **10** relax faster than any of the methyl groups, despite their apparently greater freedom for segmental motion. In particular, the normalized relaxation rate of the *ortho* methoxyl group in **3** is 39% faster than that of the *ortho* methyl group in **2**, the most closely analogous compound. The origin of this rate enhancement is not clear at present.

Conclusions.

The proton relaxation data reported here clearly evidence the transfer of relaxation contribution between the protons of the aryl ring and the C-3 methylene protons of the isoindolinone ring. Although this cannot be interpreted in terms of a unique conformational model, it is clear that such inter-ring relaxation offers a new source of structural data which warrants further study in other heterocyclic molecules. We suggest for this and other purposes, that R_1 values determined by the null point method are likely to be of sufficient accuracy, and that recourse to the lengthy calculations which are conventionally used, is unnecessary.

Acknowledgement.

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(10) The relaxation rates reported are "overall" rates, since the individual lines in a multiplet may have different relaxation rates (3). The ranges within multiplets appeared to be small in the present study, however, so that the error involved in an overall value is unlikely to be significant in the present qualitative evaluation.

(11) The chemical shifts were assigned by comparison with the spectra of 2,3-dimethylxylidene derivatives, using assigned ^{1}H spectra in the Sadtler Standard Spectra collection and ^{13}C spectra (12).

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