

The Application of Chlorine, Bromine, and Iodine N.M.R. Spectroscopy to the Study of Physico-chemical Processes in Liquids

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1 General Introduction

The development of n.m.r. spectroscopy has been dominated by the study of hydrogen. The great sensitivity of the technique towards the ^1H nucleus and its molecular environment, together with the ubiquity of H in organic compounds, have combined to produce a generation of high performance commercial spectrometers for such investigations. However, a considerable proportion of the other chemical elements possesses at least one isotope which has *spin*, and therefore a magnetic moment, and thus is capable, at least in principle, of study by n.m.r. No particular isotope presents such a favourable case for investigation as does the proton, and each to some extent has its own special characteristics. For this reason, the general applicability of the method to chemical problems, which provided such a powerful incentive for the development of commercial equipment for proton n.m.r. spectroscopy, has been lacking. The relative scarcity of equipment and expertise has made the investigation of other nuclei by n.m.r. piecemeal in comparison. Nonetheless, the study of ^{19}F , ^{31}P , ^{11}B , ^{14}N , and more recently ^{13}C , has become well-established. A less known and less exploited area of investigation is afforded by the halogens Cl, Br, and I. This Review surveys the basis and the achievements of the n.m.r. spectroscopy of these halogens. Only passing reference will be made to instrumental aspects of the topic.

The principle of the n.m.r. method is widely known.¹ A nucleus which has intrinsic angular momentum (spin) also possesses a magnetic moment which lies along the axis of spin. A magnetic field H_0 across the nucleus provides an axis of quantisation for the orientation of the spin and the magnetic moment, and lifts the degeneracy of the orientation levels. For a nucleus of spin I there are $2I + 1$ allowed orientations, spaced at energy intervals $\hbar\gamma H_0$, where γ is a nuclear property known as the magnetogyric ratio. A radiofrequency field of angular frequency γH_0 can promote transitions between these levels, giving rise to n.m.r. absorption.

For protons, $I = \frac{1}{2}$: thus there are only two orientation levels in the magnetic field. For many nuclei, including the Cl, Br, and I nuclei which are the subject of this survey, $I > \frac{1}{2}$. However, since the orientation levels are equally spaced, and

¹ A. Abragam, 'The Principles of Nuclear Magnetism', Clarendon, Oxford, 1961.

since transitions are allowed only between adjacent levels, there is only one Bohr frequency condition $\omega = \gamma H_0$ for each nucleus, and we need not further consider the magnitude of the spin quantum number (see, however, quadrupole effects, below).

The sensitivity of a nuclide to the n.m.r. experiment is determined² by the size of the energy separation of the nuclear orientation levels. This is proportional to the applied field for each species, and Table 1 shows the size of this energy separation at a constant field of 1T for various nuclear species. It should be noted that increasing the field for a given species not only increases the resonance frequency but also enhances the population difference between the upper and lower levels, which is governed by a Boltzmann distribution. This increases the net absorption of energy by the system at resonance. It is the relatively large energy separation of the nuclear spin levels of the proton at a given field strength compared with most other nuclei which makes the n.m.r. absorption of protons so strong. The relative sensitivities of the halogen nuclei (compared with the proton, at constant field) are also given in Table 1.

Table 1 Nuclear properties of naturally-occurring n.m.r.-active halogen isotopes compared with those of hydrogen^a

Isotope	Natural abundance %	Resonance freq/MHz at 1T ^b field	Sensitivity at const. field rel. to H = 1.000	Ground state nuclear spin (ħ)	Nuclear electric quad. moment/ barns ^c ($e \times 10^{-24} \text{ cm}^2$)
¹ H	99.985	42.5759	1.000	$\frac{1}{2}$	0
² D	0.015	6.53566	9.65×10^{-3}	1	2.77×10^{-3}
¹⁹ F	100.00	40.055	0.833	$\frac{1}{2}$	0
³⁵ Cl	75.53	4.1717	4.70×10^{-3}	3/2	-7.89×10^{-2}
³⁷ Cl	24.47	3.472	2.71×10^{-3}	3/2	-6.21×10^{-2}
⁷⁹ Br	50.54	10.667	7.86×10^{-2}	3/2	0.33
⁸¹ Br	49.46	11.498	9.85×10^{-2}	3/2	0.28
¹²⁷ I	100.00	8.5183	9.34×10^{-2}	5/2	-0.69

^a Source: K. Lee and W. A. Anderson, *Handbook of Chemistry and Physics*, Edn. 50, 1969-70, Chemical Rubber Company, Cleveland, Ohio;

^b 1T = 10^4 Oe;

^c Considerable uncertainty exists in the values of some of the nuclear quadrupole moments.

To a large extent the ¹⁹F resonance displays a closely similar character to the proton resonance, and many commercial proton spectrometers are convertible to record ¹⁹F spectra simply by altering the frequency range of the sample probe. The principal cause of the similarity is that the ¹⁹F nucleus has a spin of $\frac{1}{2}$ and is therefore immune to the powerful influences of quadrupole interactions which dominate the n.m.r. signals observed in the remaining halogens. It is for this reason that the scope of the present survey does not include ¹⁹F n.m.r., a topic already widely discussed.

² H. D. W. Hill and R. E. Richards, *J. Sci. Instr. (J. Phys. E.)*, 1968, 977.

The most striking feature of the resonances of ^{35}Cl , ^{37}Cl , ^{79}Br , ^{81}Br , and ^{127}I by comparison with typical proton resonances is that they have very large linewidths. The natural linewidth of a proton signal from a liquid specimen of a simple organic compound is a small fraction of 1 Hz, so that in practice the observed linewidth is usually governed by the resolution of the spectrometer. The width of the spectral line is inversely proportional to the lifetime of the nuclear spin orientational state, which for protons in stable covalent environments is typically one second or more. In turn, the relaxation processes arise from fluctuating magnetic fields in the neighbourhood of the nucleus. For nuclei which possess an electric quadrupole moment (that is, nuclei with spin quantum numbers I greater than $\frac{1}{2}$) another, and generally very powerful, relaxation mechanism is afforded by interactions of this quadrupole moment with fluctuating *electric field gradients* in the nuclear environment. For such nuclei, this relaxation interaction is usually dominant and it leads to relaxation times considerably shorter than those observed from protons, linewidths usually being much wider than the frequency resolution of the spectrometer.

For halogen nuclei which are participating in covalent bonds, the chemical bond itself produces a very powerful electric field gradient (eq) to which the electric quadrupole moment of the nucleus (eQ) is coupled. The energy of this coupling is that measured by pure nuclear quadrupole resonance (n.q.r.) spectroscopy.³ Now in a liquid the nuclear orientational states are stationary in the laboratory frame of co-ordinates, whilst the electric field gradient generated by the chemical bond is fixed in the frame of the molecule, and tumbles with it. Simple relaxation theory predicts that the relaxation time T_2 of the nucleus (of spin I) in the n.m.r. experiment is given by

$$T_2^{-1} = \frac{3}{40} \frac{2I + 3}{I^2(2I - 1)} \left(1 + \frac{\tilde{\eta}^2}{3} \right) \left(\frac{e^2 Qq}{\hbar} \right)^2 \tau_c = A \left(\frac{e^2 Qq}{\hbar} \right)^2 \tau_c \quad (1)$$

where $\tilde{\eta}$ is the n.q.r. asymmetry parameter and τ_c is a *correlation time*, i.e. a length of time which is a measure of the timescale of the molecular motion. For normal mobile liquids τ_c is of the order of 10^{-12} s. It is found that for halogen nuclei in covalent bonds the nuclear relaxation times are very short, of microsecond magnitude, so that linewidths are very large, measured typically in kHz rather than in tenths of Hz, as for protons. This makes covalent halogen n.m.r. experimentally demanding as, for example, the chemical shifts become difficult to measure with any precision. However, the short relaxation time of covalently bound halogen can be turned to advantage in the study of systems involving exchange between a covalent and an ionic site; this aspect of halogen n.m.r. will be taken up in some detail in Section 5.

It is in the study of the chloride, bromide, and iodide ions that halogen resonance has been most exploited, for here the strong electric field gradient of the covalent bond has been replaced by the essentially spherical distribution of the closed shell, so that to a first approximation there is no quadrupole coupling

³ E. A. C. Lucken, 'Nuclear Quadrupole Coupling Constants', Academic, London, 1969.

at the nucleus. In practice, there is still a measure of quadrupole interaction as a result of motion outside the ion and of perturbation of the structure of the ion itself. The quadrupole relaxation times for the ions are increased by a factor of about a thousand. Whereas the ^{35}Cl chloride ion linewidth from an aqueous solution of NaCl is *ca.* 10 Hz, the linewidth of the resonance from pure liquid CCl_4 is *ca.* 10 kHz.

2 Covalent Compounds of Cl, Br, and I

With the exception of ^{35}Cl , data for the halogen isotopes listed in Table 1 (apart from ^{19}F) in covalent compounds are almost non-existent. A few relaxation times are known indirectly from chemical exchange experiments. The small amount of ^{35}Cl shift and relaxation time data collected over the years has recently been substantially supplemented by the work of Saito⁴ and of Johnson, Hunt, and Dodgen.⁵ Both shifts and relaxation times are known for a good proportion of the liquid inorganic chlorine compounds and for a few simple chloro-organics. An attempt is made in Table 2 to gather together all this data, together with subsidiary data (quadrupole coupling constant, asymmetry parameter) frequently required in their analysis.

A. Relaxation Times.—Equation (1) may be applied to obtain a rotational n.m.r. correlation time τ_c , provided that the quadrupole coupling constant is known and provided also that the solid state value derived from n.q.r. spectroscopy may be applied to the liquid phase. There is no reason to doubt that such coupling constants are accurate to ± 2 –3% in most cases, a considerably higher degree of precision than that to which the relaxation times are known. The effect of the asymmetry parameter is often small, and in the absence of an experimental value it may be ignored to a first approximation. It is a peculiarity of spin 3/2 nuclei that $\tilde{\eta}$ cannot be obtained simply from the zero-field n.q.r. powder spectrum, and consequently asymmetry parameters have been assigned to ^{35}Cl field gradient tensors in only a few molecules. It should not be assumed that the influence of the factor $(1 + \tilde{\eta}^2/3)$ on the nuclear relaxation rate is always negligible. Such derived correlation times have been calculated by O'Reilly and Schacher^{5a} and by Johnson, Hunt, and Dodgen,⁵ and similarly computed values are included in Table 2. These correlation times may be compared with the predictions of a variety of formulae, such as the Debye–Stokes–Einstein equation

$$\tau_c = \frac{4\pi a^3 \eta}{3kT} \quad (2)$$

in which the controlling parameters are the molecular hard-sphere volume a^3 , the bulk viscosity η , and the absolute temperature T . As Johnson, Hunt, and Dodgen have shown, the functional dependence of the correlation time upon

⁴ Y. Saito, *Canad. J. Chem.*, 1965, **43**, 2530.

⁵ K. J. Johnson, J. P. Hunt, and H. W. Dodgen, *J. Chem. Phys.*, 1969, **51**, 4493.

^{5a} D. E. O'Reilly and G. E. Schacher, *J. Chem. Phys.*, 1963, **39**, 1768.

Table 2A ^{35}Cl relaxation times, chemical shifts, and n.m.r. correlation times†

Molecule	T/K	Shift/p.p.m.	T_2/ms	$e^2Qq\hbar^{-1}/\text{MHz}$	τ_c/ps	Ref.	Comments
AsCl_3	299 ± 1	-150 ± 60	0.023 ± 0.001	50.3	4.4	<i>f</i>	
AsCl_3			0.017 ± 0.002		5.9	<i>h</i>	
CrO_2Cl_2	299 ± 1	-603 ± 13	0.107 ± 0.001	31.4	2.4	<i>f</i>	
CrO_2Cl_2			0.09		2.9	<i>a</i>	
CH_3Cl	R	-40	0.099	68.1	0.55	<i>a</i>	
CH_3COCl	R	-200	0.066	(57.4)	1.2	<i>a</i>	quadrupole coupling constant estimated
CH_2Cl_2	R	-220	0.042	72.0	1.2	<i>a</i>	
CH_2Cl_2		-280				<i>c</i>	
CHCl_3	R	-410	0.025	76.7	1.8	<i>a</i>	
CHCl_3			0.034		1.3	<i>b</i>	
CHCl_3	298		0.024		1.8	<i>f</i>	
CHCl_3	373		0.040		1.1		$\Delta E^\ddagger 1.4 \pm 0.1$ kcal mol $^{-1}$
CHCl_3			0.028 ± 0.003		1.6	<i>h</i>	
CHCl_3		-450				<i>c</i>	
CCl_4	R	-560	0.020	81.2	2.0	<i>a</i>	$\tilde{\eta} = 0$
CCl_4	299 ± 1	-500 ± 100	0.025		1.5	<i>f</i>	
CCl_4			0.018 ± 0.001		2.1	<i>h</i>	
CCl_4		-730				<i>c</i>	
CCl_4	298		0.022		1.8	<i>f</i>	
CCl_4	373		0.034		1.1		$\Delta E^\ddagger 1.3 \pm 0.1$ kcal mol $^{-1}$
$\text{C}_6\text{H}_5\text{Cl}$	R		0.013	69.2	4.1	<i>a</i>	$\tilde{\eta} = 0.1$
$\text{C}_6\text{H}_5\text{Cl}$	298		0.013		4.1	<i>f</i>	
$\text{C}_6\text{H}_5\text{Cl}$	373		0.023		2.3		$\Delta E^\ddagger 1.5 \pm 0.4$ kcal mol $^{-1}$
$\text{ClO}_3^-(\text{aq.})$	298		0.016	59.3	4.4	<i>f</i>	
$\text{ClO}_3^-(\text{aq.})$	373		0.029		2.4		$\Delta E^\ddagger 1.5 \pm 0.4$ kcal mol $^{-1}$
$\text{ClO}_3^-(\text{aq.})$	R	-1050	0.024		3.0	<i>a</i>	
$\text{ClO}_4^-(\text{aq.})$	299 ± 1	-946 ± 6	5.1 ± 0.2	(0)		<i>f</i>	
$\text{ClO}_4^-(\text{aq.})$	R	-1000				<i>a</i>	
Cl_2	299 ± 1		0.041 ± 0.003	109	0.52	<i>f</i>	
Cl_2	R	-310	0.037		0.58	<i>a</i>	
Cl_2	206	-130 ± 150	0.013		1.7	<i>g</i>	
Cl_2	220	-340 ± 150	0.016		1.3		
Cl_2	235	-340 ± 150	0.019		1.1		
Cl_2	298	-370 ± 75	0.031		0.70		$\Delta E^\ddagger 1.1$ kcal mol $^{-1}$

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Molecule	T/K	Shift/p.p.m.	T_2 /ms	e^2Qqh^{-1} / MHz	τ_c /ps	Ref.	Comments
Cl ₂ (aq.)	300	-430 ± 75	0.014	109	1.5	<i>g</i>	
Cl ₃ ⁻ (aq.)	298	-150 ± 150	0.015 ± 0.004	51 ± 5	6.4	<i>g*</i>	terminal atom central atom (determined indirectly from kinetic measurements)
		-150 ± 150	0.003 ± 0.001	116 ± 8	6.3		
GeCl ₄	299 ± 1	-170 ± 60	0.041 ± 0.002	51.4	2.3	<i>f</i>	
PCl ₃	299 ± 1	-370 ± 90	0.060 ± 0.005	52.2	1.6	<i>f</i>	
PCl ₃			0.034 ± 0.002		2.7	<i>h</i>	
PCl ₃			0.040		2.3	<i>b</i>	
POCl ₃	299 ± 1	-430 ± 56	0.027 ± 0.001	57.9	2.8	<i>f</i>	
PSCl ₃	299 ± 1	-530 ± 90	0.027 ± 0.002	~60	2.6	<i>f</i>	
S ₂ Cl ₂	299 ± 1	-480 ± 96	0.022 ± 0.002	71.6	2.3	<i>f</i>	
SbCl ₅	299 ± 1		0.016 ± 0.002	55.7	5.1	<i>f</i>	
SiCl ₄	299 ± 1	-174 ± 7	0.079 ± 0.003	40.8	1.9	<i>f</i>	
SiCl ₄			0.063 ± 0.004		2.4	<i>h</i>	
SiCl ₄			0.050		3.0	<i>a</i>	
SnCl ₄	299 ± 1	-120 ± 60	0.022 ± 0.001	48.2	5.0	<i>f</i>	
SnCl ₄			0.019 ± 0.002		5.8	<i>h</i>	
SOCl ₂	299 ± 1	-660 ± 40	0.038 ± 0.001	64.0	1.6	<i>f</i>	
SO ₂ Cl ₂	299 ± 1	-760 ± 50	0.030 ± 0.001	75.4	1.5	<i>f</i>	
TiCl ₄	299 ± 1	-840 ± 30	0.400 ± 0.010	12.2	4.3	<i>f</i>	
TiCl ₄	298		0.401		4.3	<i>j</i>	
			0.552		3.1		ΔE [†] 1.0 ± 0.1 kcal mol ⁻¹
TiCl ₄			0.3		5.7	<i>a</i>	
VCl ₄	285	see comments	0.077			<i>e</i>	T-dependent Fermi contact contribution to chemical shift. Probably not pure quadrupole relaxation
VOCl ₃	299 ± 1	-791 ± 12	0.161 ± 0.001	23.1	3.0	<i>f</i>	
VOCl ₄			0.13			<i>a</i>	

†Quadrupole coupling constants taken from E. A. C. Lucken, 'Nuclear Quadrupole Coupling Constants,' Academic Press, New York, 1969.

R signifies room temperature.

Table 2B ^{37}Cl relaxation times and n.m.r. correlation times†

Molecule	T_2/ms	e^2Qqh^{-1}/MHz	τ_c/ps	Comments
CH_3Cl	0.137	53.6	0.64	
CH_3COCl	0.129	(45.2)	0.96	quadrupole coupling constant based on estimated value for ^{35}Cl
CH_2Cl_2	0.079	56.7	1.0	
CHCl_3	0.049	60.4		
CCl_4	0.042	63.9	1.2	
$\text{ClO}_3^-(\text{aq.})$	0.047	46.7	2.5	
Cl_2	0.073	85.8	0.47	

† Calculated from the data of Y. Saito, *Canad. J. Chem.*, 1965, **43**, 2530. All data relate to room temperature. Quadrupole coupling constants are calculated from ^{35}Cl data compiled by E. A. C. Lucken, 'Nuclear Quadrupole Coupling Constants', Academic Press, New York, 1969.

Table 2C ^{81}Br and ^{79}Br relaxation times†

Molecule	T/K	$T_2/\mu\text{s}$	e^2Qqh^{-1}/MHz	τ_c/ps	Ref.	Comments
CdBr^+		0.10			κ	^{81}Br
		0.07				^{79}Br
CdBr_4^{2-}		0.17			κ	^{81}Br
		0.12				^{79}Br
HgBr_4^{2-}	300	0.027 ± 0.003	322	3.6	ι	^{81}Br . Estimated quad. c.c. τ_c calculated at 298K $\Delta E^\ddagger 4.8 \pm 0.6 \text{ kcal mol}^{-1}$
HgBr_4^{2-}		0.14			κ	^{81}Br
		0.10				^{79}Br . The same T_2 values were assigned to HgBr_3^-
ZnBr^+		$0.07 \leq T_2 \leq 1.0$			κ	^{81}Br and ^{79}Br
ZnBr_4^{2-}		0.25			κ	^{81}Br
		0.17				^{79}Br

† All data estimated indirectly from n.m.r. exchange experiments.

$a^3/\eta T$ is excellently borne out by experiment, but the absolute values of the calculated τ_c are *ca.* ten times too large.

This set of experimental correlation times is perhaps the most extensive for any class of compounds known unambiguously at the present time. The method of combining the quadrupole coupling constant with the nuclear relaxation time in the manner of equation (1) is direct and simple. The great mass of n.q.r. data now available makes it particularly appropriate for halogen compounds. Recent advances⁶⁻⁹ suggest that n.m.r. relaxation techniques of this kind may provide more detailed information than simply a single correlation time, giving for

⁶ W. T. Huntress, jun., *Adv. Magn. Resonance*, 1970, **4**, 1.

⁷ D. E. O'Reilly, *J. Chem. Phys.*, 1968, **49**, 5416.

⁸ W. T. Huntress, jun., *J. Phys. Chem.*, 1969, **73**, 103.

⁹ D. L. Hogenboom, D. E. O'Reilly, and E. M. Peterson, *J. Chem. Phys.*, 1970, **52**, 2793.

example access to the finer details of the anisotropy of molecular translation and rotation.

Table 2D ^{127}I relaxation times†

Molecule	T/K	$T_2/\mu\text{s}$	e^2Qqh^{-1} MHz	τ_c/ps	Ref.	Comments
$\text{Hg}(\text{H}_2\text{O})\text{I}_3^-$ (aq.)	300	0.21 ± 0.05			^l	
HgI_4^-	300	0.11 ± 0.03	(840)	14	^l	estimated e^2Qqh^{-1} . $\Delta E^\ddagger 4.2 \pm 0.2 \text{ kcal mol}^{-1}$

†Data estimated indirectly from n.m.r. exchange experiments.

^a Y. Masuda, *J. Phys. Soc. Japan*, 1956, **11**, 620; ^b J. M. Winter, *Compt. rend.*, 1959, **249**, 1346; ^c E. L. Muetterties and W. D. Phillips, *Adv. Inorg. Chem. Radiochem.*, 1962, **4**, 231; ^d Y. Saito, *Canad. J. Chem.*, 1965, **43**, 2530; ^e D. W. Pratt and R. J. Myers, *J. Chem. Phys.*, 1969, **50**, 555; ^f K. J. Johnson, J. P. Hunt, and H. W. Dodgen, *J. Chem. Phys.*, 1969, **51**, 4493; ^g C. Hall, D. W. Kydon, R. E. Richards, and R. R. Sharp, *Mol. Phys.*, 1970, **18**, 711; ^h C. Hall, D. W. Kydon, R. E. Richards, and R. R. Sharp, *Proc. Roy. Soc. A*, 1970, **318**, 119; ⁱ P. Diehl, *Helv. Phys. Acta*, 1956, **29**, 219; ^j D. E. O'Reilly and G. E. Schacher, *J. Chem. Phys.*, 1963, **39**, 1768; ^k H. G. Hertz, *Z. Elektrochem.*, 1961, **65**, 36; ^l D. E. O'Reilly, G. E. Schacher and K. Schug, *J. Chem. Phys.*, 1963, **39**, 1756.

B. Chemical Shifts.—The interpretation of the chemical shifts of this group of compounds is in a less satisfactory state than that of the relaxation times. The chemical shift (or the shielding constant) of a nucleus in a molecule is a measure of changes induced by the polarising magnetic field H_0 in the electronic structure of the molecule. Consequently its calculation is very complicated, and rigorously requires knowledge of the ground and excited state wavefunctions. A relatively simple practical equation has been given by Saika and Slichter¹⁰ for the shift of the ^{19}F resonance in the F_2 molecule relative to the free ion, and this has provided the basis for the discussion of the ^{35}Cl shifts in covalent compounds also, as for example in the analogous case of Cl_2 .¹¹ Saika and Slichter give the following expression for the dominant contribution to the shielding constant:

$$\sigma = -\frac{2}{3} \left(\frac{e^2 \hbar^2}{m^2 c^2} \right) \Delta E^{-1} \left\langle \frac{1}{r^3} \right\rangle_{np} \quad (3)$$

ΔE is a mean molecular excitation energy, which effectively expresses the accessibility of states above the ground state. The quantity $\langle r^{-3} \rangle_{np}$ is the expectation value of r^{-3} for the valence p -electron, and is not easily calculated. Johnson, Hunt, and Dodgen⁵ sought (by arguments based on this equation and the Townes–Dailey theory³ of quadrupole coupling constants), to express the ^{35}Cl shifts in terms of e^2Qq/h , an accurately-known independent experimental parameter, obtaining:

$$\sigma \propto (e^2Qq/h) \Delta E^{-1} \left\langle \frac{1}{r^3} \right\rangle_{3p} \quad (4)$$

¹⁰ A. Saika and C. P. Slichter, *J. Chem. Phys.*, 1954, **22**, 26.

¹¹ C. Hall, D. W. Kydon, R. E. Richards, and R. R. Sharp, *Mol. Phys.*, 1970, **18**, 711.

Unfortunately the mean excitation energy is not clearly defined. It is generally true that the compounds containing transition metal ions which have relatively low-lying excited states but rather small quadrupole coupling constants show notably large chemical shifts (for example, VOCl_3 , VCl_4 , and TiCl_4 : Table 2). Furthermore, there is a general trend in the direction of larger shifts in compounds with large quadrupole coupling constants. However, there are clear anomalies: the series CH_3Cl , CH_2Cl_2 , CHCl_3 , and CCl_4 is known to show very little variation of electronic spectrum between its members,¹² such that changes in ΔE may be confidently regarded as a minor factor in the origin of the shift. The quadrupole coupling constants vary also by only a few per cent; yet very large shifts occur between CH_3Cl and CCl_4 . One possible explanation is that there is a contribution to the chemical shift from interactions between nonbonded atoms which does not reveal itself in the quadrupole coupling constant. For example, the shift difference between CH_3Cl and CCl_4 may largely be attributed to changes in $\langle r^{-3} \rangle_{3p}$ (assumed by Johnson, Hunt, and Dodgen to be constant) brought about by Cl . . Cl overlap interactions. It can be seen that this is generally in line with the data of Table 2.

3 Halogen Ion Resonances

When an alkali-metal halide salt is dissolved in water the magnetic resonance spectrum of the anion nucleus consists of a single line. Although there are many different instantaneous configurations of the particles in the liquid, the nucleus moves around in the solution very rapidly through continually changing surroundings, and on the n.m.r. timescale experiences only the average environment. A single-line spectrum suffers from a lack of information content compared with the complexity of the liquid state from which it derives. The spectrum is in fact described by just three parameters: one absolute resonance frequency at a particular field, usually measured as a chemical shift relative to a standard resonance; one linewidth parameter T_2 (the shape function is always Lorentzian); and, trivially, one intensity factor. The last is proportional to the number of resonating nuclei in the sample, and apart from occasional analytical applications rarely provides in halogen n.m.r. any information not known to the experimenter. The theory of halogen ion resonances is concerned with the dependence of the shift and linewidth parameters on variables such as the concentration of salt, temperature, solvent, ionic strength, the nature of the counterion, and so on. The combination of theory and experiment in these simple systems can improve our knowledge of ion-ion and ion-solvent encounters, and provides an essential foundation on which kinetic and biological applications of halogen n.m.r. are attempted.

The magnetic resonance frequency of a halide ion nucleus in solution differs from that of a free nucleus. The motion of the electrons of the ion induced by the magnetic field serves to reduce the field experienced by the nucleus itself. On the other hand, perturbations of the electron state of the ion as a result of its inter-

¹² C. R. Zobel and A. B. F. Duncan, *J. Amer. Chem. Soc.*, 1955, **77**, 2611.

actions with forces in its neighbourhood may cause deshielding effects or enhancements of the magnetic field strength at the nucleus. The relative shifts between various situations in which the ^{81}Br nucleus is found are shown in Figure 1. The standard state to which many measurements on ion resonances in

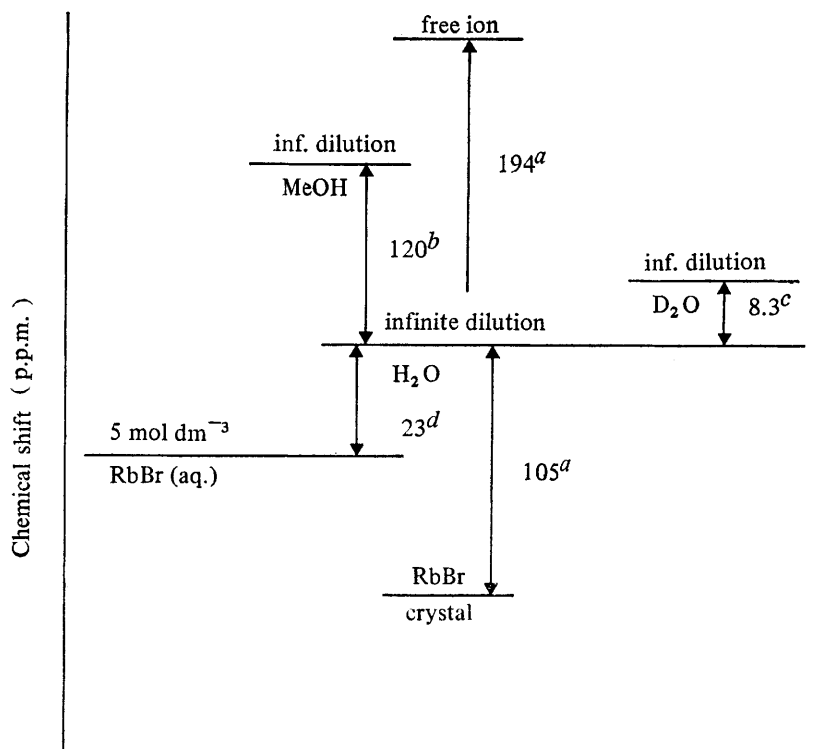


Figure 1 Br^- chemical shifts (positive values to high field) in various states. (Where shift is cation dependent, RbBr values have been used).

^a D. Ikenberry and T. P. Das, *Phys. Rev.*, 1965, **138A**, 822. ^b C. Hall, G. L. Haller, and R. E. Richards, *Mol. Phys.*, 1969, **16**, 377. ^c A. Loewenstein, M. Shporer, P. C. Lauterbur, and J. E. Ramirez, *Chem. Comm.*, 1968, 214. ^d C. Deverell and R. E. Richards, *Mol. Phys.*, 1969, **16**, 421.

solution are referred to is that of infinite dilution. This state, though conceptually convenient, is not experimentally very accessible as the sensitivity of halogen n.m.r. has hitherto precluded measurements below *ca.* 0.1 mol l^{-1} and long extrapolations of the experimental data are required.

The following two sections describe briefly the dominant features of the halide ion resonances in simple solutions. This area of research has recently been fully reviewed by Deverell,¹³ and is described only in outline here.

¹³ C. Deverell, *Progr. N.M.R. Spectroscopy*, 1969, **4**, 235.

A. Chemical Shifts.—The isothermal concentration dependence of the chemical shift of the ^{81}Br resonance for a number of alkali-metal and alkaline earth bromides in water is shown in Figure 2. The two chief features of the data are

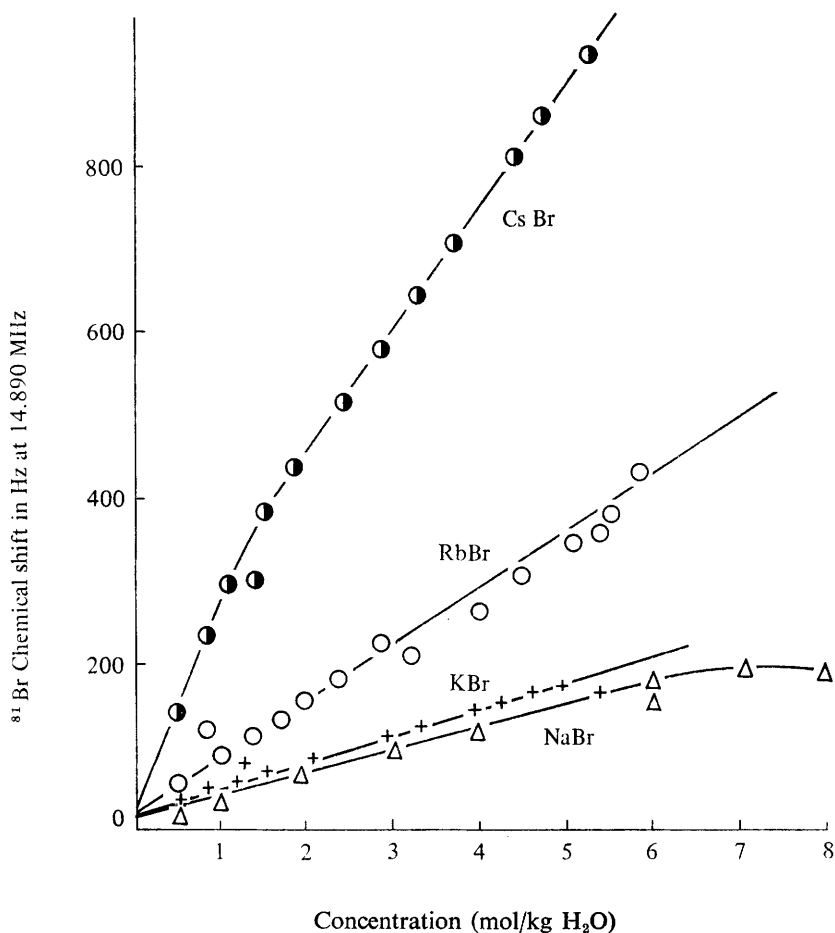


Figure 2 ^{81}Br shifts in solutions of alkali metal bromides. (Positive values are to low field.)
From C. Deverell and R. E. Richards, *Mol. Phys.*, 1969, 16, 421.

that the shift is approximately linear in salt concentration only at higher concentrations and that the slope of the plot is markedly dependent on the identity of the counterion. It should be noted that all data refer to concentrated solutions. Nonetheless, the validity of the infinite dilution extrapolation is supported by the fact that the data for different salts do extrapolate to a common value. Deverell

and Richards¹⁴ demonstrated from their results on aqueous solutions that there is a uniformity in the effect of different counterions on the nuclear resonance frequencies of the halide ions. Thus the efficacy of the cations in producing low field shifts in the halide ion resonances may be ordered $\text{Na} < \text{K} < \text{Li} < \text{Rb} < \text{Cs}$. Studies on solutions containing two alkali-metal cations mixed in various proportions demonstrated that the effects of the cations in shifting the anion resonances are roughly additive and independent. It was suggested that the origin of these ion shifts lay in the direct binary interactions of the halide ion with the metal counterion. The contribution to the shift from any interaction of the halide ion with the solvent water molecules and with other halide ions was assumed to be approximately constant with changing concentration. (At very high concentrations, anion-anion interactions must be anticipated.)

Since the larger ions cause greater shifts than the smaller ions the effect is not ascribed to a direct electrostatic (polarisation) interaction but rather to the repulsive overlap of the closed-shell ion orbitals.¹⁵ This mechanism was suggested by Kondo and Yamashita¹⁶ to account for the shifts of the ions in alkali halide crystals. Deverell and Richards presented convincing evidence in its support in the case of salt solutions. Detailed calculations¹⁷ of the magnitudes of the shifts anticipated for various mechanisms have fully supported this conclusion.

At concentrations of salt less than *ca.* 3 mol kg⁻¹, Deverell and Richards¹⁴ found some evidence of departure from linearity in the plots of shift against concentration, although the experimental accuracy did not enable this to be firmly established. The much more precise measurements later made on the ¹³³Cs nucleus¹⁷ allowed similar curvature in a cation resonance to be characterised with considerable precision. It was shown that it could be accounted for quantitatively on the basis of a model founded on a Debye-Hückel radial distribution function and is caused by an electrostatic clustering of unlike ions in the ionic atmosphere of a halide ion. This leads to a non-linear concentration dependence of the inter-ionic collision probability. Some measurements on ³⁵Cl of chloride ion have accurately established¹⁷ the curvature in the shift *versus* concentration plot in aqueous CsCl and suggest that the same explanation is appropriate (Figure 3). The degree of clustering and thus the degree of curvature in the plot depends on the dielectric constant of the solvent and the temperature. Halliday, Richards, and Sharp demonstrated that the curvature of the ¹³³Cs and ³⁵Cl ion shifts is such that the shift δ obeys an interesting concentration law, which may be written in the following form:

$$\delta - \delta_0 = D'c^g$$

where δ_0 is the infinite dilution shift; g depends on the dielectric constant and the temperature; and D' is a constant depending on the ion, counterion, and

¹⁴ C. Deverell and R. E. Richards, *Mol. Phys.*, 1969 **16**, 421.

¹⁵ C. Deverell and R. E. Richards, *Mol. Phys.*, 1966, **10**, 551.

¹⁶ J. Kondo and J. Yamashita, *J. Phys. Chem. Solids*, 1959, **10**, 245.

¹⁷ J. D. Halliday, R. E. Richards, and R. R. Sharp, *Proc. Roy. Soc.*, 1969, **A313**, 45.

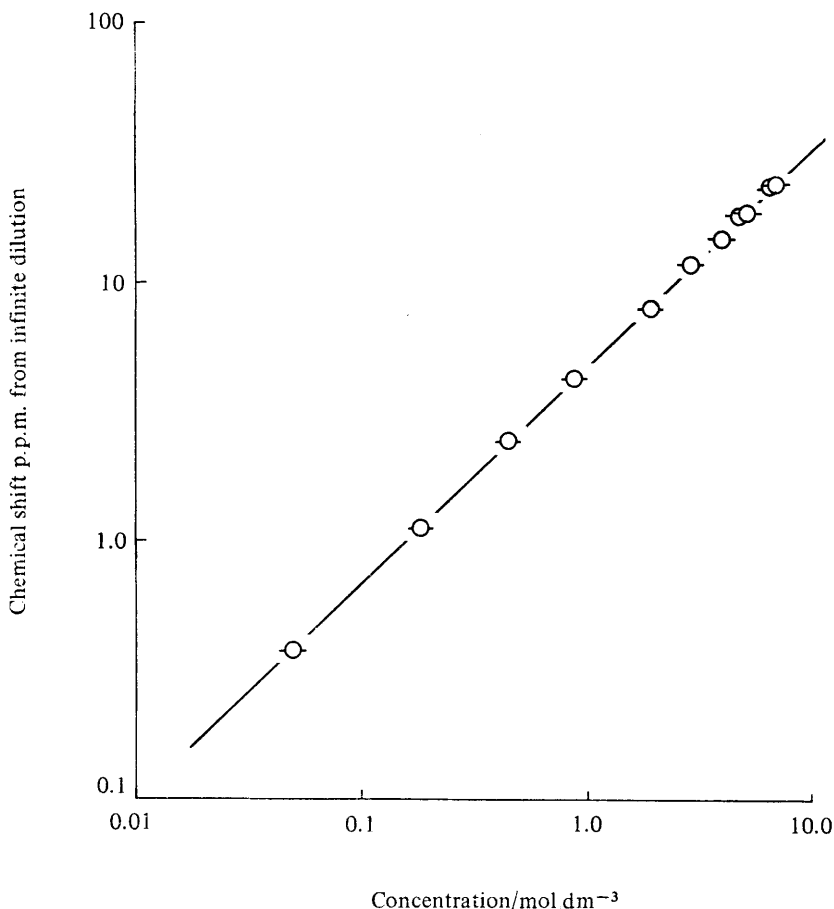


Figure 3 Full logarithmic plot of concentration dependence of ^{35}Cl ion chemical shifts in aqueous CsCl . Continuous line is theoretical plot, adjusted to experimental points only at 0.5 mol dm^{-3} . From J. D. Halliday, R. E. Richards, and R. R. Sharp, *Proc. Roy. Soc.*, 1969, **A313**, 49.

probably the solvent. For aqueous solutions at 25°C , g is found to be *ca.* 0.7, in good agreement with calculation. That g is considerably less than 1 accounts for the earlier observation of Deverell and Richards that the shifts in dilute solutions appear more nearly linear when plotted against ion activities than concentrations. The law given above is only an approximate representation of the complete theoretical expression, but is a highly accurate approximation in the molal concentration range 0.001 to 1 for water, largely because of the high dielectric constant. Its range is more restricted in solvents of lower dielectric constant.

Serious error may be incurred by using this rather than the complete expression as a basis for obtaining infinite dilution shifts δ_0 .¹⁸

It may be anticipated that measurements of shifts of halide ions down to low concentrations will provide a sensitive measure of ion-ion encounters and data against which to test ionic distribution functions and theories of such phenomena as ion-pairing. At the present time there are almost no examples of halogen n.m.r. at sufficiently low concentrations for the theory of dilute electrolyte solutions to be applied. However, signal averaging techniques and improved spectrometer stabilities are rapidly combining to extend the experimental range.

At the opposite end of the concentration scale, the data, though easy to obtain, are harder to interpret. Deverell,¹⁴ for example, has demonstrated that the ³⁵Cl shift in LiCl (which is soluble in water up to *ca.* 18 molal) passes through a pronounced maximum at *ca.* 8 molal, the turn-over setting in at *ca.* 5.5 molal. These facts receive an acceptable explanation if it is assumed that the Li⁺ ion is surrounded by rather firmly-bound water molecules which prevent Li⁺-Cl⁻ encounters until the supply of water molecules available for Li⁺ co-ordination is exhausted. The Li⁺-Cl⁻ overlap integral can be expected to be very small, thus giving a dramatic high-field shift. Similar effects are found in LiBr solutions in water, and in both LiCl and LiBr solutions in water-methanol mixtures.¹⁹

At the present stage of development, n.m.r. study of concentrated solutions of this type is inevitably frustrated by our inability to relate the data with an adequate theory of solutions. A similar observation may be made on the application of such methods to simple ionic melts, where neither the dynamics nor the distribution of the particles is well understood. In some respects it may be an easier task to unravel magnetic resonance phenomena in concentrated solutions by first studying molten salt systems of simple composition (preferably monatomic ions) than as a modification of dilute solution effects. It is, after all, the interaction of the ions with the water solvent molecule which is the most poorly understood aspect of aqueous systems.

B. Ion-Solvent Interaction.—Although the free ion frequencies are difficult to estimate at all accurately, there is no doubt (as shown in Figure 1) that the infinite dilution ion resonance frequency in water is shifted a long way from the free ion value. Transfer of the ion from water to methanol or heavy water also causes relatively large shifts.^{19,20} Unfortunately, very few solvent shift data of this kind are available for the halide ions: the interested reader is referred to the work on ¹³³Cs⁺¹⁷ and ²³Na⁺²¹ ion resonance studies for examples of the magnitude of such solvent shifts in other ions. Such scanty halide data as exist are gathered together in Table 3.

At present there is almost no understanding of the origin of these shifts: it

¹⁸ C. Hall, R. E. Richards, and R. R. Sharp, to be published; C. Hall, D.Phil. thesis, Oxford, 1970.

¹⁹ C. Hall, G. L. Haller, and R. E. Richards, *Mol. Phys.*, 1969, **16**, 377.

²⁰ A. Loewenstein, M. Shporer, P. C. Lauterbur, and J. E. Ramirez, *Chem. Comm.*, 1968, 214.

²¹ E. G. Bloor and R. G. Kidd, *Canad. J. Chem.*, 1968, **46**, 3425.

Table 3 Halide ion infinite dilution shifts (*p.p.m.*) relative to water at 25 °C.

	³⁵ Cl	⁸¹ Br	¹²⁷ I	Reference
D ₂ O	4.7 ± 0.3	8.3 ± 0.3	13.2 ± 2.5	<i>a</i>
MeOH	60	120		<i>b</i>
DMSO	-65			<i>c</i>
MeCN	-33			<i>c</i>
Me ₂ NCHO	-42			<i>c</i>
MeNO ₂	-14			<i>c</i>

Positive values are high-field shifts.

^a A. Loewenstein, M. Shporer, P. C. Lauterbur, J. E. Ramirez, *Chem. Comm.*, 1968, 214;

^b C. Hall, G. L. Haller, and R. E. Richards, *Mol. Phys.*, 1969, **16**, 377; ^c C. H. Langford and T. R. Stengle, *J. Amer. Chem. Soc.*, 1969, **91**, 4014.

would be surprising if repulsive overlap contributions are not important, but specific interactions such as hydrogen bond formation to X⁻ and van der Waals' forces may make contributions. The measured shift depends directly on the interaction between the monatomic probe ion and the solvent molecules and contains information of profound interest. It should be relatively easy to accumulate data of this type with present equipment. In this area pragmatic correlation of shifts with chemical and molecular properties may provide the only reasonable approach at present. We may certainly expect the following factors to be important:

- (i) molecular volume—packing geometry about an ion
- (ii) specific interactions of ion with solvent, H-X⁻;
- (iii) charge transfer to solvent;²² electron-donor capacity of solvent;²¹
- (iv) large atoms with large overlap integrals in the solvent molecule;
- (v) charge distribution within the solvent molecule

C. The Relaxation Times.—The chemical motive for studying nuclear magnetic relaxation times is the desire to learn more of the microscopic motions in the neighbourhood of the nucleus. As was briefly indicated in the Introduction, the theory of such relaxation allows us to relate the observed relaxation time to a function of a correlation time. However, it is an experimental problem to decide to what motion in the liquid the correlation time refers; there may be a number of additive contributions such that equation (1) should be generalised to

$$T_2^{-1} = A \sum_i \left(\frac{e^2 Q q}{\hbar} \right)_i^2 \tau_{c_i} + B \sum_j A_j \tau_{c_j'} \quad (5)$$

where the second sum of contributions refers to other possible relaxational mechanisms (such as the magnetic dipolar interaction). The complicated nature of electrolyte solutions (even of simple aqueous alkali-metal halide systems) at the molecular level makes this a major concern and research so far has been aimed at elucidating the mechanism of relaxation of the halide and other simple ion

²² C. H. Langford and T. R. Stengle, *J. Amer. Chem. Soc.*, 1969, **91**, 4014.

nuclei. The situation is further complicated by the absence of any knowledge of the quadrupole coupling constant, which for more or less any mechanism must itself be an average over many configurations. Here we see a sharp contrast with the simpler case of ^{35}Cl relaxation in, for example, CCl_4 , where the quadrupole coupling constant is a fixed tensor in the molecular frame, whose components are measurable by nuclear quadrupole resonance spectroscopy (see Section 2). The ion, however, experiences many field gradients from various particles in its neighbourhood, all of which are random functions of time; that is not to say that they may not be correlated. It is extremely probable that at least some of the motions of the water molecules in the region of an ion are correlated, that is they are not mutually independent. This complication has hitherto been largely ignored in discussions of these phenomena.

The two characteristic n.m.r. relaxation times T_1 and T_2 which describe the decay of induced magnetisation along and perpendicular to the polarising magnetic field are equal for the ion resonances in simple solutions. This is expected in a situation where all the motional processes effecting relaxation are very rapid compared with the nuclear Larmor frequency.¹ Both linewidth and spin-echo and other transient methods can be used to determine the relaxation time.

(i) *Infinite Dilution Relaxation Times of Ion Nuclei.* Hertz²³ and Valiev²⁴ have attempted to calculate from elementary principles the relaxation time of a quadrupolar nucleus having no stable solvation sphere. Both assumed that the other ions and the solvent molecules constitute point sources of an electric field gradient at the ion nucleus which fluctuates as a result of the microdynamic motion in the solution. The calculation was cumbersome and introduced some parameters difficult to assign. Nonetheless, the correct order of magnitude was obtained for relaxation of $^{35}\text{Cl}^-$, $^{81}\text{Br}^-$, and $^{127}\text{I}^-$ in water.

In contrast, many of the studies in this area have been concerned with attempts to correlate the ion nuclear relaxation with other possible measures of the motional correlation time in the solution, for example with the viscosity η or with η/T ,¹³ or the self-diffusion coefficient²⁵ and dielectric relaxation time.²⁶ Thus there is now plenty of evidence that ion relaxation is intimately linked with the solution viscosity—or that both the viscosity and the motion causing ion relaxation depend upon related processes in the solution. The finding²⁶ that the infinite dilution relaxation time (like the dielectric relaxation time in the presence of salts) is proportional to η/T , but has a smaller activation energy, suggested that the dominant contribution to the relaxation from solvent molecules may come from the rather disorganised outer solvation regions. These are the regions of structural mismatching between the bulk water and the water oriented about the ion, where the rotation or reorientation of the solvent may be relatively free.

²³ H. G. Hertz, *Z. Elektrochem.*, 1961, **65**, 20.

²⁴ K. A. Valiev, *J. Exp. Theor. Phys.*, 1960, **10**, 77.

²⁵ M. St. J. Arnold and K. J. Packer, *Mol. Phys.*, 1968, **14**, 241.

²⁶ C. Hall, R. E. Richards, G. W. Schulz, and R. R. Sharp, *Mol. Phys.*, 1969, **16**, 529.

Unfortunately there are few data on other solvents. Hall, Haller, and Richards¹⁹ reported the ³⁵Cl and ⁸¹Br relaxation times in water-methanol mixtures, and found that the addition of methanol to the aqueous lithium salt solutions greatly enhanced the relaxation rate. This result was tentatively associated with a relatively long dielectric relaxation time in methanol.

(ii) *Concentration and Temperature Dependence of Ion Relaxation Times.* The semi-empirical equation²⁶

$$T_2^{-1} = [Ac_{\text{H}_2\text{O}} + B(c)]\eta/T + D \quad (6)$$

is generally successful in relating the temperature and concentration dependence of ⁷⁹Br, ⁸¹Br, and ²³Na ion relaxation times in H₂O. The constant *D* depends only upon the ion and the solvent, and its magnitude determines how great will be the difference in activation energy of T_2^{-1} and η/T . It may be considered as a structural parameter and is probably associated with the organisation of the solvent around the ion in question. *B(c)* apparently describes the influence of the other ions on the relaxation time: it is approximately linear in the concentration variable, and, so far as can be seen from the rather rough data, is determined by the counterion. The larger counterions make much larger contributions than the smaller ones, as was found for the shifts; a feature which led Devereil¹³ to suggest that thermal modulation of the repulsive overlap shift interaction was the source of the ion-ion contribution to the relaxation. On the other hand, the evidence³ of nuclear quadrupole coupling constants of the alkali-metal halide ion pairs shows that in the gas phase the field gradients increase with *decreasing* metal ion radius. If this is true also in solution then the explanation of the large effect of large ions such as Cs⁺ on the halide ion relaxation times should perhaps be sought in long correlation times rather than strong interactions. In addition, the large counterion may cause a greater distortion and disruption of the hydration zone of the central ion during a collision than would a smaller ion. Alternatively, the rôle of the counterion may be to destroy, during interionic collisions, the approximately centrosymmetric organisation of the solvent molecules about the central ion. Thus there is created a net field gradient whose actual origin lies largely or partly in the solvent molecules about the central ion rather than simply in the counterion itself.

4 Paramagnetic Systems

A number of interesting and complicated phenomena appear in the n.m.r. spectra of systems containing paramagnetic ions or molecules. Although these effects have been widely studied in proton and fluorine resonances,²⁷ the influence of electron paramagnetism on the other halogen resonances has received little attention.

The unpaired electron has a magnetic moment 1846 times that of the proton, and thus generates a relatively very large fluctuating dipolar field in solution. Coupling to this field usually provides a powerful relaxation mechanism for the

²⁷ D. R. Eaton and W. D. Phillips, *Adv. Magn. Resonance.*, 1965, 1, 103; E. de Boer and H. van Willigen, *Prog. N.M.R. Spectroscopy*, 1967, 2, 111.

nuclei, causing marked reductions in both T_1 and T_2 . This mechanism works most efficiently when the lifetime of the unpaired electron state is long compared with the correlation time (molecular tumbling or chemical exchange) governing nuclear relaxation. In most cases the motion of the molecules in the liquid reduces the time-average of this dipolar field so that there is no shift in the nuclear resonance frequency. In some circumstances, where the g tensor of the unpaired electron is anisotropic ($g_{\parallel} \neq g_{\perp}$), a resultant *dipolar* or *pseudocontact* shift may be observed.

In addition to this simple through-space effect, the unpaired electron may be delocalised and actually have a finite spin density at the nucleus under observation. This amounts to saying that the unpaired electron has a degree of s - or σ -character with respect to the nucleus. Under these circumstances there is a *Fermi-contact shift* of the nuclear resonance frequency. This is, of course, precisely the same hyperfine interaction which reveals itself in the electron spin resonance spectrum of an unpaired electron which is scalar-coupled to a magnetic nucleus. Besides generating the contact shift, the hyperfine interaction may also make a contribution to the nuclear relaxation, since both electron spin relaxation and chemical exchange processes cause fluctuations in the coupling at the nucleus. Finally, the field gradient about the free electron may couple with the nuclear electric quadrupole moment of a nucleus with spin $I > \frac{1}{2}$ to afford another relaxation mechanism.

Contact shifts can be used to obtain electron spin densities (with signs) at the nucleus observed, and thus provide data of interest in bonding theory. Relaxation time studies on the effect of paramagnetic additives on the n.m.r. spectra of other species in solution give information on the distance of approach and the association of the paramagnetic species and the nucleus. The rapid relaxation of a nucleus bound to a paramagnetic ion or molecule may be used to advantage in kinetic studies of chemical exchange processes.²⁸ Examples of such experiments are to be found in the literature: a recent instance is provided by the ^{19}F n.m.r. study of Stengle and Langford²⁹ on the nature of the outer co-ordination sphere of various paramagnetic Cr^{III} complexes. In one of the few papers on ^{35}Cl n.m.r. in paramagnetic systems, Chesnut³⁰ investigated the shift caused by addition of quantities of Co^{2+} ions, and interpreted the results in terms of complex equilibria. The effects of 'inert' cations were attributed to competition with the Co^{II} complexes for hydration water.

Shulman³¹ studied both ^{35}Cl and ^{14}N shifts in Cl^- and CN^- solutions containing Cu, Fe, and Mn. A simple ligand field model precludes hyperfine interaction at the ^{14}N nucleus for the hexacyano-complexes of Fe^{III} , Mn^{III} , and Cr^{III} complexes, and the observed shifts in the Fe and Mn complexes were ascribed to anisotropic g tensors of the species caused by Jahn-Teller distortion. In the Cu^{II}

²⁸ T. J. Swift and R. E. Connick, *J. Chem. Phys.*, 1962, **37**, 307.

²⁹ T. R. Stengle and C. H. Langford, *J. Phys. Chem.*, 1965, **69**, 3299.

³⁰ D. B. Chesnut, *J. Chem. Phys.*, 1960, **33**, 1234.

³¹ R. G. Shulman, *J. Chem. Phys.*, 1958, **29**, 945.

and Fe^{II} chloro-complexes, however, no anisotropy is expected and the shift in this case appears to be due to σ -bonding between the metal ion and Cl^- .

5 Study of Chemical Exchange

The determination of rate constants from measurements of the nuclear relaxation times of the quadrupolar nuclei of Cl, Br, and I has not received much attention in the past, although the study of ^{17}O has been developed for this purpose.²⁸ At present the method is restricted to obtaining information on rapidly-established equilibrium systems. The method of the exchange-modified Bloch equations³² is ideally suited to these quadrupolar nuclei.

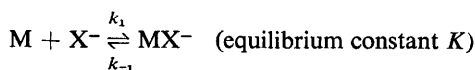
If a halide ion in solution is involved in one or more exchange equilibria, it occupies successively two or more sites which each bestow on the nucleus their characteristic resonance frequencies and relaxation times. One limiting case is that in which exchange is quenched or made indefinitely slow. Then the observed spectrum consists of the superimposition of the spectra of each site, weighted by their relative populations. As the lifetimes of the nuclei in each site are allowed to become shorter the process of exchange begins to interfere with the processes of relaxation in each site, causing every nucleus to begin to experience features of both sites. In the limit of very fast exchange, the observed spectrum is indistinguishable from that expected if every ion occupied a number-average site. In the intermediate region, the values of the relaxation and shift parameters derived from the spectrum are functions of the exchange rate constants between the sites and the relaxation and shift parameters of each site. In simple cases (such as 2- or 3-site exchange with one dominant species), the modified Bloch equations can be rearranged and solved analytically as a function of the rate constants for some parameter, such as an absorption linewidth increment. This might be defined as,

$$\Delta = \left(\frac{1}{T_2} \right) - \left(\frac{1}{T_{2a}} \right) = \pi(\Delta\nu - \Delta\nu_a) \quad (7)$$

where $\Delta\nu$ is an observed linewidth at half-height and $\Delta\nu_a$ is the linewidth of the dominant species (here usually the halide ion) in the absence of exchange, and T_2 and T_{2a} are the corresponding relaxation times. In more complicated systems the equations are solved numerically for particular values of the parameters, including the rate constants, and the theoretical spectrum generated point by point. This procedure is virtually mandatory where the dominant species assumption breaks down, since the spectrum is no longer well described as a single Lorentzian line, except in the fast exchange limit, and cannot be characterised by a single parameter such as Δ .

As a simple example of an exchange process which may be easily treated, consider the case where the halide ion X^- binds reversibly to a species M:

²⁸ C. S. Johnson, jun., *Adv. Magn. Resonance*, 1965, **1**, 33.



The dominant species assumption $[MX^-] \ll [X^-]$ allows a general expression for Δ to be written in terms of the rate constants.

$$\Delta = k_1[M] \left\{ \frac{\left(\frac{1}{T_{2b}} + k_{-1} \right) \frac{1}{T_{2b}} + \Delta\omega_b^2}{\left(\frac{1}{T_{2b}} + k_{-1} \right)^2 + \Delta\omega_b^2} \right\} \quad (8)$$

In this equation a denotes the X nucleus in the X^- site, and b the X nucleus in the MX site. $\Delta\omega_b$ is the chemical shift of the b site relative to the a site.

In the *fast exchange limit* (where the chemical rate processes are much more rapid than the relaxation processes or the relative Larmor precession of the two sites)

$$\Delta = \frac{[MX^-]}{[X^-]} \frac{1}{T_{2b}} \quad (9)$$

Thus the excess broadening of the X^- n.m.r. line is simply proportional to the 'bound' fraction of X^- .

In the case of *very slow exchange*

$$\Delta = k_1[M]$$

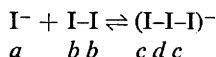
and the excess broadening is proportional to the *forward* rate constant k_1 . However, this semi-limiting form is usually applicable only when Δ is very small and the excess broadening experimentally difficult to detect. Of course, in the true slow exchange limit of $k_1 = 0$, $\Delta = 0$.

The dominant species assumption is not an especially restrictive condition for many situations of interest, such as exchange of halide ion ligands with metal ions, or biological binding sites. In any event, the two-site and other exchange cases can be solved numerically without such assumptions. The limitations of the n.m.r. method, are, however, illustrated by the above expressions; rate information can only be obtained in the intermediate exchange domain, which, loosely, is where the processes of exchange are either comparable with the difference in the nuclear Larmor frequencies of the sites or else interrupt the processes of nuclear spin relaxation in each site. Further, the parameters T_2 and ω characteristic of each of the sites are required input. This is often not possible for experimental (chemical or instrumental) reasons. However, a series of measurements in which the concentration or temperature dependence is investigated, or in which more than one isotope is studied, may in principle be used to determine the problem.³³

Of the quadrupolar halogen nuclei, ^{127}I typically exhibits the shortest relaxation time, and can provide rate information in the region of nanosecond kinetics.

³³ C. Hall, D. W. Kydon, R. E. Richards, and R. R. Sharp, *Proc. Roy. Soc.*, 1970, **A318**, 119.

Meyers³⁴ and later Genser³⁵ have both studied the iodine-tri-iodide equilibrium by means of ¹²⁷I n.m.r. and both obtained kinetic constants to support the view that the equilibrium is established at a diffusionally limited rate. No covalent iodine resonance has been observed directly but the I⁻ line in water is about 1kHz wide and is increased by the addition of I₂. The tri-iodide equilibrium is a four-site problem



although a full modified Bloch equation analysis of the analogous trichloride ion equilibrium³³ shows that little inaccuracy would result from combining sites *c* and *d* into an average trihalide ion site.

Undoubtedly the most useful kinetic results yet obtained from halogen n.m.r. are those of Hertz,³⁶ who studied the complex equilibria of Br⁻ with Hg²⁺, Zn²⁺, and Cd²⁺. He made use of the fact that in systems containing two isotopes of the same element (notably ³⁵Cl, ³⁷Cl; ⁷⁹Br, ⁸¹Br) comparative measurements of the linewidths of each isotope can be used to establish the value of T_{2Bk-1} , where B represents the bound Br⁻ site. More generally, the ratio of the linewidth increments of two isotopes *a* and *b* (of quadrupole moment Q_i and spin I_i) changes sigmoidally from a value of unity at low exchange rates to a limiting fast exchange value:

$$\frac{\Delta_a}{\Delta_b} = \frac{A_a}{A_b} \left(\frac{Q_a}{Q_b} \right)^2$$

where

$$A_i = \frac{3}{40} \left(\frac{2I_i + 3}{I_i^2(2I_i - 1)} \right)$$

This provides essentially a differential method of investigating equilibrium kinetics.³³

6 Biological Applications

Although biological applications of halogen n.m.r. involve no new principles, it is convenient to discuss them separately. At present, the study of biochemical and biophysical processes and systems by magnetic resonance techniques is a rapidly expanding field. The new generation of high-field 220 MHz spectrometers has brought great advances in the high resolution proton resonance study of macromolecules.³⁷ In addition, a number of laboratories have reported halogen n.m.r. studies using the 'halide ion probe' technique originally described by Stengle and Baldeschwieler,³⁸ and with which this section of the present review is concerned.

We have discussed earlier the way in which halide ion linewidths are increased

³⁴ O. E. Meyers, *J. Chem. Phys.*, 1958, **28**, 1027.

³⁵ E. E. Genser, *U.S. At. Energy Comm.*, 1962, UCRL-9846.

³⁶ H. G. Hertz, *Z. Elektrochem.*, 1961, **65**, 36.

³⁷ J. J. M. Rowe, J. Hinton, and K. L. Rowe, *Chem. Rev.*, 1970, **70**, 1.

³⁸ T. R. Stengle and J. D. Baldeschwieler, *Proc. Nat. Acad. Sci. U.S.A.*, 1966, **55**, 1020.

by rapid exchange with covalent sites in which they have short relaxation times, and equation (9) shows that (in the fast exchange limit) the observed linewidth is simply the mean of the linewidths of each site weighted by their respective populations. However, as mentioned in Section 1, a short relaxation time may be caused as well by a long correlation time as by a large field gradient [as is obvious from equation (1)]. Thus, the rapid reversible binding of ions to macromolecules, which have typically thousandfold longer correlation times than simple oligatomic molecules, can produce large broadenings of ion linewidths, even though the interaction may be more electrostatic than covalent in nature. If both a large field gradient and a very long correlation time characterise the binding site then the effect can be dramatic. In favourable cases the addition of one part in 10^5 of macromolecular binding site to a halide solution can give rise to detectable linebroadening of the ion resonance.

Stengle and Baldeschwieler³⁸ pointed out in 1966 that Hg^{2+} ions will bind to reactive or exposed sulphhydryl groups of proteins. The Hg tag then provides a possible co-ordination site for halide ions, and provided exchange is rapid the halide ion resonance is broadened. So long as certain kinetic conditions are satisfied, then knowledge of the solution composition enables the relaxation time of the halide ion nucleus at the binding site to be determined. When the quadrupole coupling constant of the nucleus in the site can be estimated, then the rotational correlation time may be calculated. Variation of conditions such as pH and temperature or the addition of other substances to the system reveals changes in the accessibility of the binding site to the Cl^- ions.

Furthermore, the n.m.r. linebroadening may be used simply as a convenient monitoring observable in a titration experiment. For example, measurement by Stengle and Baldeschwieler of the ^{35}Cl linewidth increment as HgCl_2 was added to a chloride solution containing small amounts of haemoglobin, showed that there are two reactive $-\text{SH}$ groups per haemoglobin to which the Hg binds.

Several other studies of this sort have made use of Hg binding to exposed S-atoms on proteins. For example, Haugland *et al.*³⁹ investigated a hapten-antibody interaction using 2,4-dinitro-4'-(chloromercury)diphenylamine hapten. Bryant⁴⁰ observed the helix-coil transition in synthetic poly-L-glutamate labelled at the terminal amide function with *N*-acetyl-DL-homocystein thio-lactone, which then bonds to Hg^{2+} .

The halide ion probe technique has recently been extended to systems other than Hg-labelled molecules. Ward⁴¹ has investigated the binding of Cl^- to a Zn metalloenzyme, carbonic anhydrase, under various conditions. He showed that the Cl^- binding (or at least that revealed by n.m.r. linebroadening) occurs specifically at the active site and found that known enzyme inhibitors such as cyanide reduce the broadening almost to zero. He further showed that the

³⁹ R. P. Haugland, L. Stryer, T. R. Stengle, and J. D. Baldeschwieler, *Biochemistry*, 1967, **6**, 498.

⁴⁰ R. G. Bryant, *J. Amer. Chem. Soc.*, 1967, **89**, 2496.

⁴¹ R. L. Ward, *Biochemistry*, 1969, **8**, 1897.

apoenzyme (the enzyme without the metal) is twenty-five times less effective in causing Cl^- linebroadening than the native enzyme.

A promising field of study is that of metal ion complexation with ATP and other nucleotides.⁴²

Some evidence⁴³ has been put forward in support of non-specific binding of halide ions by proteins in ways quite unrelated to metal ion sites. An example of ⁸¹Br n.m.r. in this field indicated sharp differences in this respect between Br⁻ and Cl^- binding with carbonic anhydrase.

A survey list of halide ion studies of biomolecules is presented in Table 4.

Table 4 *Biological applications of halogen n.m.r. (except ¹⁹F)*

<i>N.m.r. nucleus</i>	<i>Metal ion</i>	<i>Biomolecules studied</i>	<i>Reference</i>
³⁵ Cl	Hg	haemoglobin	<i>a</i>
³⁵ Cl	Hg	haptent-antibody interactions	<i>b</i>
³⁵ Cl	Hg, Cd, Zn	bovine mercaptalbumin	<i>c</i>
³⁵ Cl	Zn	carbonic anhydrase	<i>d</i>
⁸¹ Br		lysozyme, α -chymotrypsin, seralbumin, ceruloplasmn, alcohol dehydrogenase, carbonic anhydrase	<i>e</i>
³⁵ Cl	Zn	Zn nucleotide diphosphate complexes	<i>f</i>
³⁵ Cl	Zn	Zn ADP complexes	<i>g</i>
³⁵ Cl	Hg	ferric peroxidase, myoglobin, haemoglobin	<i>h</i>
³⁵ Cl	Hg	synthetic poly-L-glutamate	<i>i</i>
³⁵ Cl	Hg	α -chymotrypsin	<i>j</i>

^a T. R. Stengle and J. D. Baldeschwieler, *Proc. Nat. Acad. Sci. U.S.A.*, 1966, **55**, 1020; *J. Amer. Chem. Soc.*, 1967, **89**, 3045; ^b R. P. Haugland, L. Stryer, T. R. Stengle, and J. D. Baldeschwieler, *Biochemistry*, 1967, **6**, 498; ^c R. G. Bryant, *J. Amer. Chem. Soc.*, 1969, **91**, 976; ^d R. L. Ward, *Biochemistry*, 1969, **8**, 1897; ^e M. Zeppezauer, B. Lindman, S. Forsén, and I. Lindqvist, *Biochem. Biophys. Res. Comm.*, 1969, **37**, 137; ^f J. A. Happe and R. L. Ward, *J. Amer. Chem. Soc.*, 1969, **91**, 4096; ^g R. L. Ward, and J. A. Happe, *Biochem. Biophys. Res. Comm.*, 1967, **28**, 785; ^h W. D. Ellis, H. B. Dunford, and J. S. Martin, *Canad. J. Biochem.*, 1969, **47**, 157; ⁱ R. G. Bryant, *J. Amer. Chem. Soc.*, 1967, **89**, 2496; ^j A. G. Marshall, *Biochemistry*, 1968, **7**, 2450.

⁴² R. L. Ward and J. A. Happe, *Biochem. Biophys. Res. Comm.*, 1967, **28**, 785.

⁴³ M. Zeppezauer, B. Lindman, S. Forsén, and I. Lindqvist, *Biochem. Biophys. Res. Comm.* 1969, **37**, 137.