The Use of Various Nuclei as Probes in a New NMR Method for Obtaining Proton/Deuteron Fractionation Data

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Abstract: An extension to the new NMR spectroscopic method (Jarret, R. M.; Saunders, M. *J. Am. Chem. Soc.* **1985**, *107*, 2648) for rapidly and conveniently obtaining isotopic fractionation factors of substrates undergoing rapid proton-deuteron exchange, with solvent water (H_2O, HOD, D_2O), through the observation of ^{13}C spectra is presented. The intrinsic isotope shift of nuclei near the sites of isotopic incorporation is the basis of this procedure, which has the unique capability of simultaneously measuring the exchange constants for isotopic exchange of several different groups in the same molecule. In this report, ^{1}H, ^{7}Li, ^{11}B, ^{14}N, ^{17}O, ^{19}F, ^{23}Na, ^{31}P, ^{35}Cl, ^{37}Cl, ^{39}K, ^{79}Br, ^{81}Br, and ^{127}I are examined and the utility of each as probes in the application of this technique is evaluated. A wider variety of compounds have thus been opened to experimental investigations, using this new method.

For the isotopic exchange reaction

$$HA + DB \underset{}{\overset{K_{frac}}{\rightleftharpoons}} DA + HB \qquad (1)$$

the equilibrium constant K_{frac} is known as the fractionation factor. Since the discovery of deuterium, methods have been devised to measure the concentrations of the isotopically related species and determine isotope exchange equilibrium constants. Most of these methods are unable to measure equilibria directly in dilute aqueous solutions and are not applicable when more than one exchangeable group is present in the molecule.

The introduction of an isotope, in particular the ready introduction of deuterium, into a molecule induces changes in the NMR chemical shift positions (intrinsic isotope shifts) for nuclei near the substituted atom. The size of this effect decreases with increasing through-bond distance between the site of isotopic substitution and observed nucleus. If an equilibrium is established between partially deuterated solvent and substrate (each containing a readily exchangeable proton) such that the proton/deuterium exchange is slow on the NMR time scale, nuclei adjacent to the site of exchange will appear as a doublet in the NMR spectrum (such as with an amide dissolved in a mixture of H_2O and D_2O).[1] One peak of the doublet corresponds to the protonated molecule, while the second peak corresponds to the deuterated molecule; the integrations identify the amounts of each species present in solution. With proton/deuterium exchange that is rapid on the NMR time scale (as found with most alcohols, thiols, amines, acids, etc. in water), a single peak is seen in the NMR spectrum that appears in a position somewhere between the extreme chemical shifts, corresponding to the fully protonated or fully deuterated species. The observed chemical shift is then an indicator of the proportion of protonated and deuterated species in solution. Observing the shifts of systems in pure H_2O and pure D_2O as well as in solutions containing known mixtures of H_2O and D_2O (and HOD), undergoing rapid proton/deuteron exchange, allows ready determination of fractionation factors.[2]

Assuming that activities are proportional to concentration,

$$K_{frac} = \frac{[\text{solute D}][\text{solvent H}]}{[\text{solute H}][\text{solvent D}]} \qquad (2)$$

for the case where proton/deuterium exchange is fast on the NMR time scale,

$$K_{frac} = \frac{F_{av}[\text{solvent H}]}{(F_{D_2O} - F_{av})[\text{solvent D}]} \qquad (3)$$

All frequencies are referred to the signal of the substance in H_2O taken as zero, F_{av} is the averaged NMR frequency in the H_2O/D_2O mixture, and F_{D_2O} is the frequency (corrected to complete deuteration of solute) in pure D_2O. This corresponds to the intrinsic isotope chemical shift and a minor contribution from the surrounding solvent isotope. Rearrangement of terms to the following form allows for convenient graphical display (see Figure 1).

$$\frac{F_{av}}{F_{D_2O}} = \frac{K_{frac}}{(\%\text{ H solvent}) + [K_{frac}(\%\text{ D solvent})]}(\%\text{ D solvent}) \qquad (4)$$

We present here an extension of our recently reported method, for determining fractionation factors with NMR spectroscopy, to the observation of nuclei other than ^{13}C. We can in these systems still study simultaneously the deuterium fractionation factors between water and *each* unique exchangeable site in a molecule (provided exchange is rapid on the NMR time scale). The number of substrates suitable for this technique is thereby considerably increased.

Experimental Section

All substrates examined (except the phosphorus containing compound supplied by Dr. Hägele) were used as purchased or purified by standard means.[3] The 99.8% D_2O used in sample preparation was obtained, and used without further purification, from MSD Isotope Co. Phosphoric acid was generated by cautiously dissolving phosphorus pentoxide in water (H_2O or D_2O) to obtain samples, free from trace paramagnetic impurities. Adjustment of pH (to control the extent of ionization) was performed by the appropriate addition of H_2SO_4 or D_2SO_4 (from Aldrich Chemical Co.) during sample preparation. Stock solutions, of concentrations necessary to give good signal to noise in the NMR spectra in relatively few scans, were made by dissolving each compound in distilled H_2O and in D_2O. The H_2O/D_2O mixtures were prepared by combining appropriate convenient amounts (measured by volume and mass) of aqueous stock solutions.

For consistent comparison, the H_2O solution for each compound studied was placed in the inner cell of concentric NMR tubes. The D_2O fraction in the outer cell was varied from 0 to 100%. Frequency differences between corresponding NMR signals originating from each compartment are then measured. Interchange of solutions between the two cell compartments was performed to verify that solution position has little effect on the measured chemical shift difference for the compounds studied.

For sufficient resolution to be obtained, spectral parameters are typically set so that an interval of about 0.2 Hz/point is achieved; this corresponds to a spectral width of about 3000 Hz for a 32000 point acquisition. The exact settings depend on the nucleus, natural peak widths, and peak separation. A 45-50° pulse is generally used, and

(1) Reuben, J. *J. Am. Chem. Soc.* **1986**, *108*, 1082. If exchange is slow on the NMR time scale and base line resolution between the isotopically related signals in the ^{13}C spectrum is possible, integration of the peaks provide the appropriate information to determine the isotopic fractionation factor for each exchangeable group in the molecule.

(2) Jarret, R. M.; Saunders, M. *J. Am. Chem. Soc.* **1985**, *107*, 2648.

(3) Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*, 1966.

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Table I

	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%[a]
A	3.26	5.99	8.65	11.60	14.33	17.34	20.66	24.08	27.80	31.71
B	13.77	27.19	42.20	56.14	71.39	85.85	101.86	117.18	133.65	151.09
C	10.20	19.87	30.73	41.47	52.88	64.07	76.77	89.49	103.47	118.03
D	5.39	10.40	14.80	19.60	23.63	27.78	31.80	35.90	39.78	43.92
E		0.76	1.39	2.13	1.83	2.89	3.54	4.48	4.81	5.35
F	0.51	0.88	1.20	1.53	1.89	2.22	2.61	2.76	2.96	3.26
G	0.42	0.64	0.76	0.98	1.20	1.23	1.52	1.43		1.93

B[b]

	case	nucleus	temp, K	concn, M	av K_{frac}
A	H_3PO_4/0.7 M H^+	^{31}P	300	0.5	0.86 ± 0.07
B	P3/0.14 M H^+	^{31}P	300	0.1	0.90 ± 0.01
C	P4/0.28 M H^+	^{31}P	300	0.01	0.82 ± 0.02
D	NH_4Cl	^{14}N	303	0.5	1.25 ± 0.03
E	piperazine	^{1}H	300	0.1	0.88 ± 0.23
F	methanol	^{1}H	300	0.5	1.46 ± 0.18
G	LiOH	^{7}Li	303	0.5	1.65 ± 0.45

[a] F_{D_2O}. [b] P3: 1,2-dimethyldiphosphinic acid ethyl monoester. P4: 1,2-diphosphonic acid ethyl monoester.

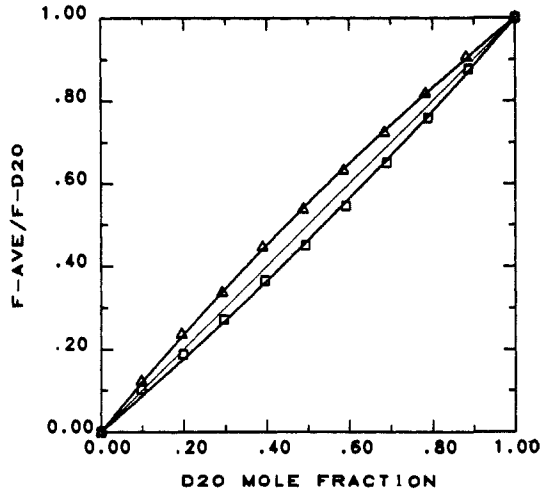

Figure 1. Triangles: ammonium chloride, K_{frac} greater than one. Straight line: theoretical K_{frac} of unity. Squares: phosphoric acid, K_{frac} less than one.

100–200 scans are accumulated for most compounds studied. To ensure maximal magnetic field homogeneity, shimming is performed on a dual cell arrangement that has the compound dissolved in the same solvent composition, in both compartments, so that a single sharp peak is observed in the Fourier-transformed spectrum.

Results and Discussion

This new technique was established with ^{13}C NMR spectroscopy for organic molecules in aqueous solution, but as indicated by the data in the tables, this technique is applicable to a wide variety of molecules, under conditions that allow for proton exchange that is rapid on the NMR time scale. The average value for K_{frac}, along with the uncertainty associated with one standard deviation, is reported (Table IB). K_{frac} obtained from a non-linear least-squares fit of the data is totally consistent with the average value calculated for each case. The χ^2 value associated with the best fit for the systems represented in the figure is on the order of 10^{-4}.

Depending on the system studied, the nucleus of choice for NMR spectroscopy may be ^{13}C, ^{31}P, ^{14}N, ^{17}O, ^{1}H, etc. Thus far, ^{13}C NMR spectroscopy has proven to be most useful. Unlike ^{13}C NMR, the measured isotopic splittings in ^{1}H NMR are quite small. As found in the ^{1}H NMR spectrum for methanol and piperazine, the maximum splitting (F_{D_2O}) for the protons α to an exchangeable site is less than 4 Hz at 500 MHz and 300 K. Since the accuracy of this technique depends on the magnitude of the intrinsic isotope shift difference (F_{D_2O} and F_{av}) for the observed signal (as well as the peak width and resolution) in the NMR spectrum, ^{1}H NMR (although a possible probe) is not as versatile or as sensitive as ^{13}C NMR, when used in this method.

Investigations, using ^{31}P NMR (at 202.4 MHz) to determine the fractionation constant for the neutral, monoanionic, and dianionic forms of phosphoric acid, have been undertaken. Although ^{31}P chemical shifts appear to be quite sensitive to the extent of ionization,[4] reliable values for K_{frac} should be obtained at selected regions of pH where one species predominates. The line width appears extremely sensitive to traces of paramagnetic impurities (addition of EDTA decreases the peak widths but unfortunately perturbs the chemical shift positions). Under controlled acidic conditions, where the neutral H_3PO_4 represents better than 99% of the phosphoric acid species, a value of 0.88 is measured for K_{frac}, a value similar to that measured for carboxylic acids. There is no significant difference in the value of K_{frac} obtained for concentrated solutions of H_3PO_4 if the sulfuric acid (to control the extent of ionization) is not added. In the ^{31}P NMR spectrum it is the deuterated species that absorbs further downfield than the protonated species, unlike the ^{13}C situation. (Since it is only the magnitude of the chemical shift difference that is used in the calculation, the relative shifts of the protonated and deuterated species have no effect on the determination of K_{frac}.) There is a large intrinsic isotope chemical shift difference of more than 30 Hz for phosphoric acid (see Table IA). This large splitting reduces to about 8 Hz when the predominant species is the monoanion (whether obtained from titration of H_3PO_4 or direct examination of the commercially available potassium salt). For the dianion (potassium salt), the splitting returns to a healthy 30 Hz or so. The measured peaks are broad for both ionic forms of phosphoric acid mentioned, due to the presence of trace paramagnetic impurities. Without further purification, a reliable K_{frac} value for the monoanion cannot be obtained, since the ratio of maximum splitting to peak width is relatively small. However, the fractionation factor of 0.92 found for the dianion agrees well with the value of 0.91 reported by Kresge.[5]

Acidified solutions of several phosphonic and phosphinic acids have also been examined. There is indication of internal hydrogen bond formation in 1,2-diphosphonic acid ethyl monoester and to a lesser extent in 1,2-dimethylphosphinic acid ethyl monoester. The measured values for K_{frac} of 0.82 and 0.90 are significantly lower than values (of approximately unity) measured for acids incapable of internal hydrogen bonding, such as methylphosphinic acid. The difference between resonances for dicyclohexylthiophosphinic acid in 1:1 H_2O/D_2O and in pure H_2O is actually slightly greater than the difference between resonances for the compound in pure H_2O and in pure D_2O! Since this acid is only very slightly soluble in water, we feel that dissociation is taking place to a significant extent, and as shown by Gerlt,[4] ^{31}P NMR chemical shifts do not behave in a predictable fashion upon ion-

(4) Gerlt, J.; Reynolds, M.; Demou, P.; Kenyon, G. *J. Am. Chem. Soc.* **1983**, *105*, 6469.
(5) Kresge, A. J.; Tang, Y. C. *J. Phys. Chem.* **1979**, *83*, 2156.

ization of phosphinic acids. Since the extent of ionization need not be the same in H_2O as in D_2O or as in H_2O/D_2O mixtures, the chemical shifts are not only affected by the equilibrium between solute and solvent for isotope possession but are also affected by the equilibrium between neutral and ionized acid. Ionization is therefore perturbing and masking the effect due to isotopic incorporation, normally observed in the NMR spectrum. As the pH is decreased, by the addition of sulfuric acid to the sample, the value for K_{frac} approaches unity.

Measurements have also been made on alcohols, using ^{17}O NMR at 67.8 MHz. Although the peaks are inherently broad due to quadrupole coupling, the chemical shift difference between ^{17}O–H and ^{17}O–D is relatively large and isotopic splitting can be detected (80 Hz per deuterium). The use of ^{17}O NMR spectroscopy is especially attractive since the fraction of deuterium in the water could be directly monitored. An internal check on the determination of K_{frac} would then exist for molecules containing the exchangeable site OH, since the fraction of deuterium in the solute and solvent could be simultaneously measured. However, the peaks in the ^{17}O NMR spectrum which we have measured have thus far been too broad (over 130 Hz) to be of use with this technique.

Boric acid was used to test the utility of ^{11}B at 160.4 MHz, as a probe in this technique. No isotopic splitting is observed; that is, a single peak is seen in the NMR spectrum when the acid dissolved in H_2O is compared to the acid dissolved in D_2O, with the dual cell arrangement. Isotopic splitting is smaller than or comparable to the natural line width.

Additional investigations with other nuclei such as ^{23}Na at 132.3 MHz, ^{39}K at 23.3 MHz, and ^{7}Li at 194.3 MHz have been undertaken. For the potassium, sodium, and lithium cations, generated from their corresponding halide salts in aqueous solutions, as measurable chemical shift difference has been detected between samples in H_2O and samples in D_2O, in accord with Loewenstein.[6] This seems reasonable since it would be the oxygen atom of the water that would be directly surrounding the ion and therefore make little difference if the oxygen atom were part of an H_2O, HOD, or D_2O molecule. Compounds such as sodium hydroxide and potassium hydroxide do not show any splitting in the dual cell arrangement used either; that is, the intrinsic isotope chemical shift difference is small in comparison to peak width. For the potassium and sodium salts, this would indicate that there is essentially complete dissociation of the ions in water at 1 M concentration. Lithium hydroxide *does* display measurable isotopic splitting, and the resulting K_{frac} obtained was greater than one. The deuterated species, LiOD, is downfield from the protonated species, LiOH, in the ^{7}Li NMR spectrum.

Since lithium chloride in H_2O and D_2O does not display isotopic splitting in the ^{7}Li spectrum, it is believed that Li^+ of LiOH is not displaying simple preferential solvation, but rather we suspect that here, the lithium ion is serving to report about the isotopic equilibrium between OH^- and D_2O. The discovery of a measurable although small, isotopic chemical shift difference for lithium hydroxide (due to partial covalent character or strong contact ion pairing) indicated to us that ^{7}Li NMR should be useful in determining ion pairing equilibrium constants for such (non-isotopic exchange equilibria) systems as LiOH/NaCl, LiF/NaI, etc., in aqueous solution. The experimental procedure is identical with the isotope exchange experiment, but instead of proton/deuteron interchange it is the entire hydroxide and halide ion that are exchanged in H_2O. Lithium hydroxide is placed in the inner compartment and serves as the reference; the outer tube contains the particular lithium halide and the chemical shift difference measured in the ^{7}Li NMR spectrum corresponds to 100% lithium halide in H_2O. A known mixture of lithium hydroxide and the sodium or potassium halide replaces the lithium halide in the outer compartment and the chemical shift difference, with respect to the maximum splitting, represents the proportion of lithium halide to lithium hydroxide in water. The trend in equilibrium constants measured for exchange between lithium hydroxide and sodium and potassium halides was as expected. That is, the equilibrium lies in favor of association between lithium and halide and is larger for the reaction with potassium salts than with sodium salts. The degree of measured association between the lithium ion and the halide ion is largest for chlorine (with an equilibrium constant of 6.86 and 12.36 for reaction with sodium and potassium salts, respectively), intermediate for bromine (K_{eq} of 4.40 and 6.34 for reaction with sodium and potassium salts, respectively), and smallest for iodine (K_{eq} of 1.39 and 2.73 for reaction with sodium and potassium salts, respectively); the equilibrium between lithium hydroxide and sodium or potassium fluoride salts could not be evaluated since the chemical shifts for lithium fluoride and lithium hydroxide are nearly coincident (only 0.37-Hz separation).

Ammonium chloride, with tetrahedral symmetry about nitrogen, gives a relatively narrow ^{14}N line. A substantial splitting was observed at an NMR frequency of 36.1 MHz and a K_{frac} greater than unity was measured, with very little data scatter for a 0.5 M solution. The measured value for K_{frac} seems to be somewhat dependent on the concentration of ammonium chloride; the value is highest for the 0.1 M solution (1.38) and consistently decreases with increasing ammonium chloride concentration, approaching a value of 1.15 for a 2.5 M solution. The measured value for K_{frac} does not appear to vary considerably when other halide counterions are used in place of chloride at constant concentration. The NMR signal for ammonium acetate is still sharp (unlike the NMR signal for 0.5 M ammonium hydroxide), indicating the presence of the tetrahedrally symmetric ammonium ion; the measured K_{frac} is slightly lower than that of the ammonium halides at the same concentration. Addition of sulfuric acid to the 0.5 M ammonium chloride solution such that there is a concentration of acid in excess of 10^{-5} M slows the rate of exchange such that the ^{14}N NMR signal is a multiplet. At 10^{-5} M sulfuric acid, the exchange is still fast and the measured K_{frac} decreases only slightly. An attempt to do ^{15}N spectroscopy, at a NMR frequency of 50.6 Mhz, on unenriched samples of ammonium chloride failed because the signal was too weak. The ^{14}N NMR spectra of amines show only a single discernable peak when subjected to this method; the isotopic splitting is small compared to the natural peak widths.

The halides (^{35}Cl at 49.0 MHz, ^{37}Cl at 40.8 MHz, ^{79}Br at 125.28 MHz, ^{81}Br at 135.0 MHz, ^{127}I at 100.0 MHz, and ^{19}F at 188.2 MHz) have also been investigated as potentially useful probes in this study. Since the hydrogen or deuterium atoms of water are directed toward the anion, the immediate chemical environment of the anion should be substantially different when in H_2O and in D_2O. Relatively large intrinsic isotope chemical shift differences for various halide salts in aqueous solution have been measured.[6,7] The chemical shift differences we report are consistent with these earlier values. In total agreement with Lowenstein's and others'[7] findings, the measured fractionation factor for KF is essentially unity, implying that there is no preferential solvation by H_2O or D_2O about the fluoride ion. The value of K_{frac} for HF (measured in tubes fitted with Teflon liners) averaged 0.84 (see Table II) from 0.5 to 4 M (made from 50% aqueous stock solution), similar to other acids that have been studied. This indicates, as compared to KF and in contrast to HCl (see below), that HF (or $H_3O^+F^-$) remains incompletely dissociated in water at these concentrations.

Solutions of HCl (1 M, made from 37% by weight aqueous stock solution) in H_2O and in D_2O have been examined. The same value of 0.96 for K_{frac} is found when both ^{35}Cl and ^{37}Cl are used. As compared to ^{37}Cl the overall intrinsic isotope chemical shift difference is larger with ^{35}Cl NMR but the peak width is measurably greater; therefore, ^{37}Cl NMR was used in the more detailed investigations involving chloride ion. To determine if the chloride ion was behaving as a reporter nucleus for the equilibrium between HCl and DCl, or H_3O^+ and D_2O, or whether the value of K_{frac} was simply reflecting a slight preference to solvation of the ion by H_2O, comparisons were made between aqueous solutions

(6) Loewenstein, A.; Shporer, M. *Chem. Commun.* **1968**, 214.

(7) (a) Blaser, J.; Lutz, O.; Steinkilberg, W. *Z. Naturforsch.* **1972**, *A27*, 72. (b) Caldin and Gold *Proton Transfer Reactions*; Chapman and Hall: London, 1975.

Table II. Single Point NMR Data; F_{av} (δ in Hz) for Approximate D_2O Fraction

case[b]	nucleus	temp, K	concn, M	50%	100%[a]	K_{frac}
K_2HPO_4	^{31}P	300	0.5	15.53	32.82	0.92
glycerophosphate dianion	^{31}P	300	0.1	19.31	38.91	1.00
trimethyl phosphate	^{31}P	300	0.5	3.51	6.91	1.04
P1/no pH adjustment	^{31}P	300	0.1	38.40	188.75	0.30
P1/0.1 M H^+	^{31}P	300	0.1	50.32	107.72	0.88
P1/0.28 M H^+	^{31}P	300	0.1	49.21	102.68	0.94
P1/1.0 M H^+	^{31}P	300	0.1	57.43	118.18	0.96
P2/no pH adjustment	^{31}P	300	0.0007	60	60	****
P2/0.01 M H^+	^{31}P	300	0.0007	103.02	380.25	0.37
P2/0.1 M H^+	^{31}P	300	0.0007	102.70	226.90	0.83
P2/0.5 M H^+	^{31}P	300	0.0007	83.32	167.21	1.00
P3/no pH adjustment	^{31}P	300	0.1	80.48	201.69	0.67
P4/no pH adjustment	^{31}P	300	0.1	46.67	120.04	0.64
KF	^{19}F	298	1.0	269.04	538.01	1.01
KF	^{19}F	298	0.5	278.68	560.81	1.00
HF/H_2O/0.1 M H^+	^{19}F	298	0.5	449.33	1056.67	0.80
HF/H_2O	^{19}F	298	1.0	456.66	1086.59	0.84
HF/H_2O	^{19}F	298	4.0	397.28	1168.62	0.87
HCl/H_2O	^{37}Cl	303	1.0	84.49	186.27	0.96
HCl/H_2O	^{35}Cl	303	1.0	101.45	223.83	0.96
HCl/DCl	^{37}Cl	303	0.1	93.61	192.88	0.95
HCl/DCl	^{37}Cl	303	0.5	92.35	189.61	0.96
HCl/DCl	^{37}Cl	303	1.0	90.61	185.64	0.96
HCl/DCl	^{37}Cl	303	2.5	83.52	173.53	0.93
HCl/DCl-KF	^{37}Cl	303	2.5	77.13	155.03	0.95
KCl	^{37}Cl	303	0.1	94.31	193.16	0.96
KCl	^{37}Cl	303	0.5	92.53	190.45	0.95
KCl	^{37}Cl	303	1.0	92.18	187.71	0.97
LiCl	^{37}Cl	303	2.5	91.31	187.72	0.95
HCl-DCl/KCl	^{37}Cl	303	0.1	92.99	191.41	0.95
HCl-DCl/KCl	^{37}Cl	303	0.5	90.57	186.64	0.95
HCl-DCl/KCl	^{37}Cl	303	1.0	87.17	179.90	0.95
HCl-DCl/LiCl	^{37}Cl	303	2.5	80.66	166.94	0.94
NH_4Cl	^{37}Cl	303	1.0	88.99	189.35	0.89
NH_4Cl	^{14}N	303	0.1	25.59	44.41	1.38
NH_4Cl	^{14}N	303	1.0	22.76	44.06	1.16
NH_4Cl	^{14}N	303	2.5	21.71	44.90	1.15
$NH_4Cl/10^{-5}$ M H^+	^{14}N	303	0.5	23.00	43.19	1.19
NH_4I	^{14}N	303	0.5	23.53	44.16	1.20
NH_4Br	^{14}N	303	0.5	23.82	44.02	1.24
NH_4F	^{14}N	303	0.5	23.50	43.61	1.13
ammonium acetate	^{14}N	303	0.5	22.86	44.54	1.15

[a] F_{D_2O}. [b] P1: dimethylphosphinic acid. P2: dicyclohexylthiophosphinic acid. P3: 1,2-dimethyldiphosphinic acid ethyl monoester. P4: 1,2-diphosphonic acid ethyl monoester.

of HCl, KCl, and LiCl. As found in Table II, the values of K_{frac} are virtually identical for all concentrations (between 0.1 and 2.5 M) of HCl/DCl, KCl, LiCl, KCl-HCl/DCl, and LiCl-HCl/DCl solutions. Moreover, the measured splittings are very similar and appear in the same spectral region. We therefore conclude that all the spectra represent the solvated chloride ion and that the fractionation factor between the water of solvation and bulk water is not significantly affected by the counterion (H^+, K^+, or Li^+) at concentrations between 0.1 and 2.5 M. In hopes of finding the presence of the mixed halide[8] salt $[F-H-Cl]^-$ in aqueous solution, the ^{37}Cl NMR spectra of 2.5 M solutions of KF and HCl were examined, but the measured value for K_{frac} is the same as that found for HCl and chloride salts, indicating that the chloride ion is free and not involved in complex formation to a significant extent.

Although the measured intrinsic isotope chemical shift difference for 1 M aqueous solution of HBr is extremely large (about 1000 Hz), the measured peak width is about 400 Hz, making both bromine nuclei insensitive probes for this technique. With respect to peak width vs. maximum splitting, ^{81}Br NMR is somewhat better than ^{79}Br. Although isotopic splitting is observed, the use of ^{127}I NMR to examine the intrinsic isotope chemical shift difference of 1 M aqueous solutions of HI and NaI has not yielded useful results with this technique (even though the intrinsic chemical shift is greater than 1200 Hz) due to enormous peak widths (on the order of the isotopic splitting).

(8) Kreevoy, M. M.; Liang, T. M. *J. Am. Chem. Soc.* **1977**, *99*, 5207. The application of this method to the potassium bifluoride salt gave unreliable results, presumably due to isotopic perturbation by solvent water on the equilibrium between KFHF, K^+, $[FHF]^-$, KF, HF, H^+, and F^- which masks the change in chemical shift with isotopic incorporation.

Conclusions

In expanding the use of our original ^{13}C NMR method of equilibria measurement, by using other nuclei as probes, a wider variety of systems (undergoing rapid isotopic exchange) can be studied. In addition, this method has also been successfully extended to equilibria measurements in systems where non-isotopically related groups exchange.

The major feature of this technique (now extended to a wider variety of molecules) is that, with a single experiment, the fractionation factors for several unique exchangeable sites in a molecule can be simultaneously measured. That is, to a first approximation, the average NMR frequency of each nucleus (relative to its frequency when the attached exchangeable group is fully protonated or deuterated) reflects the isotopic fractionation factor for the exchangeable site directly bonded to it; this approximation increases in validity as the through-bond distance between sites increases.

Since hydrogen bonding produces substantial changes in the IR frequencies for stretching and bending, it should also affect fractionation factors significantly as these are related to zero-point energies. Therefore, if we can measure fractionation factors for molecules containing several rapidly exchanging groups using this new technique, we may be able to detect and evaluate the importance of strong internal hydrogen bonds, if they occur, in aqueous solution. These should, in turn, be related to the preferred

conformations of these molecules in solution.

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Registry No. H, 1333-74-0; ^{7}Li, 13982-05-3; ^{11}B, 14798-13-1; ^{17}O, 13968-48-4; ^{35}Cl, 13981-72-1; ^{37}Cl, 13981-73-2; ^{39}K, 14092-91-2; ^{79}Br, 14336-94-8; ^{81}Br, 14380-59-7; N_2, 7727-37-9; Na, 7440-23-5; I_2, 7553-56-2.

Electrochemical Switching in Anthraquinone-Substituted Carbon-Pivot Lariat Ethers and Podands: Chain Length Effects in Geometric and Electronic Cooperativity†

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Abstract: A series of 1-substituted anthraquinones has been synthesized, most often by nucleophilic aromatic substitution on 1-chloroanthraquinone. They have the following structures and were prepared in the indicated yields where E is $-CH_2CH_2-$ and Ar is the 1-substituted anthraquinone: **1**, Ar–OCH_3 (48%); **2**, Ar–$OEOEOCH_3$ (61%); **3**, Ar–$OEOEOEOCH_3$ (61%); **4**, Ar–$OEOEOEOEOCH_3$ (65%); **5**, Ar–$OEOEOEOEOEOCH_3$ (14%); **6**, Ar–OEOEOEO–Ar (66%); **7**, Ar–O–CH_2–15-crown-5 (39%). Both one- and two-electron time-resolved redox couples (using cyclic voltammetry) are observed for the various systems when 0–1.0 equiv of Li^+, Na^+, or K^+ are added. The electrochemical behavior is complex and is accounted for by a combination of electronic and steric factors.

Molecular switching in macrocyclic polyether systems has been the subject of intense study during the past decade. Photochemical switching has been especially well-studied in Japan by Shinkai, Ueno, Takagi, Tabushi, and others.[1] In addition, changes in pH,[2] thermally-controlled permeability.[3] and oxidation–reduction chemistry[4] have all been explored as switching mechanisms. The work conducted in our group has been primarily concerned with electrochemical switching in lariat ethers and podands having nitroaromatic sidearms[5] and more recently has been focussed on similar species derived from anthraquinones.[6] Anthraquinones differ significantly from the nitroaromatic systems in their ability to undergo discrete one- or two-electron reduction. We have previously noted that anthraquinone-substituted podands exhibit surprising geometrical effects during the electrochemical switching process.[7] We now report the details of the switching process and describe the geometrical and electronic cooperativity we have observed for the Li^+-, Na^+-, and K^+-mediated electrochemical reductions in anthraquinone-substituted podands and lariat ethers.

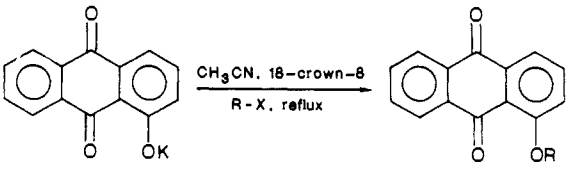
Results and Discussion

Syntheses. Three methods have been used to prepare the anthraquinone-substituted podands and lariat ethers. Method A (Scheme I) involves the reaction of the potassium salt of 1-hydroxyanthraquinone with the appropriate halide or tosylate in the presence of a solvent and 18-crown-6.

In the absence of 18-crown-6, the reaction does not give any of the desired product. This is not surprising since the potassium salt of 1-hydroxyanthraquinone, due to ion-pairing interactions, is a very poor nucleophile. Nakatsuji et al. report that reaction of the sodium salt of 1,8-dihydroxyanthraquinone with triethylene glycol ditosylate in refluxing xylene gives only 0.6% yield of the bis(anthraquinone) crown **8**.[8]

In the presence of 18-crown-6, the potassium is stripped from the anthraquinone anion increasing its nucleophilicity and giving reasonable yields of desired product. The compounds prepared by using this reaction are listed in Table I as method A.

Scheme I



30-48%

Method B (Scheme II) is a modification of the procedure reported by Krapcho and Shaw[9] and is more straightforward than

† For the previous parts in this series, see ref 5.

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