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Equilibrium Studies by Electron Spin Resonance. XIII. Determination of Ion Association Constants for Diamagnetic Salts by the Use of Electron Spin Resonance

Sir:

Since the classic work of Brauman,[1] it is well understood that solvation energies are just as important in the determination of the thermodynamic stability of anions in solution as are the intramolecular considerations. One of the most important phenomena in the determination of solvation energy is ion pairing.

Although it has been shown that ESR is the most powerful tool in the investigation of the nature of ion pairing, this technique has been limited to the study of paramagnetic salts. For diamagnetic salts a variety of experimental techniques have been employed for the determination of ion pair association constants. These include NMR,[2] visible spectroscopy,[3] and conductivity.[4] Although conductivity is clearly the most versatile, even it is often useless for the determination of ion pair dissociation constants in strongly solvating solvents like hexamethylphosphoramide (HMPA).[5] Only with difficulty can conductivity be utilized in highly solvating aprotic solvents.[6] Consequently, for a series of potassium salts, on which conductivity measurements were carried out in HMPA, only KNO_3 yielded data allowing the calculation of the ion association constant (K_a). Here we wish to describe a new and more sensitive technique for the determination of K_a of diamagnetic salts.

The reduction of 2,6-di-*tert*-butylbenzoquinone in HMPA by potassium metal results in the formation of the free anion radical, which exhibits an ESR signal consisting of a triplet due to two equivalent protons with a coupling constant of 2.346 ± 0.005 G.[7] Successive additions of potassium nitrate to this solution result in a gradual decrease in the observed coupling constant. This decrease is due to the formation of the ion pair (β), which is in rapid equilibrium with the free ion (α), eq 1.[7]

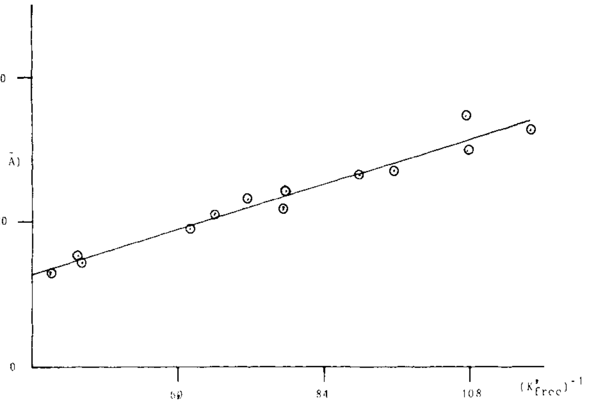

Figure 1. Plot of $1/(A^0 - \bar{A})$ vs. the reciprocal of (K^+_{free}) for the 2,6-di-*tert*-butylbenzoquinone anion radical with added potassium nitrate. The (K^+_{free}) was calculated from the total amount of dissolved potassium nitrate and the K_a of 59 ± 8 reported by Monica and coworkers.[5] This plot yields a value for the equilibrium constant controlling eq 1 of 0.076.

Table I. Observed Coupling Constant of the 2,6-Di-*tert*-butylbenzoquinone Anion Radical in HMPA at 25° with Added KNO_3[a]

$(KNO_3)_{total}$, *M*	(K^+_{free}), *M*	$\bar{A}$, G
0	0	2.346
0.0143	0.0093	2.323
0.0184	0.0111	2.319
0.0254	0.0139	2.299
0.0311	0.0160	2.294
0.0532	0.0227	2.276
0.0637	0.0255	2.270
	∞	2.05

[a] Only a representative set of data are shown.

$$\beta \rightleftharpoons \alpha + K^+ \qquad (1)$$

The observed coupling constant ($\bar{A}$) has been previously shown to be a weighted average between that for the free ion (A^0) and that for the ion pair (A').[7] This weighted average is given by

$$\bar{A} = \{(\alpha)A^0 + (\beta)A'\}/\{(\alpha) + (\beta)\} \qquad (2)$$

Combining this expression with that for the thermodynamic equilibrium constant for eq 1, $K_{diss} = (\alpha)(K^+_{free})/(\beta)$ leads to the following expression.

$$1/(\bar{A} - A^0) = K_{diss}/(K^+_{free})(A' - A^0) + 1/(A' - A^0) \qquad (3)$$

Knowing the ion association constant for KNO_3, $K_a = (K^+, NO_3^-)/(K^+_{free})(NO_3^-)$, the free potassium ion concentration can be calculated for any amount of KNO_3 that is added to the anion radical solution. A plot of the reciprocal of the potassium ion concentration free of ion pairing vs. $1/(\bar{A} - A^0)$ should be linear and have a slope of $K_{diss}/(A' - A^0)$ and an intercept of $1/(A^0 - A')$. Treated in this manner our data did yield a straight line, Table I, Figure 1.

Each time the experiment is performed, a sample is first taken without the addition of salt, then salt is dissolved and another sample is taken. Using the dual cavity technique, the sample containing added salt is placed in one cavity and the standard without added salt in the other. The coupling constant for the sample containing salt is then accurately determined by comparison with the standard sample, which is assigned a coupling constant of exactly 2.346 G.

KNO_3 is the only salt for which K_a is known in HMPA. However, a salt with an unknown K_a can now be added to the anion radical solution and the coupling constant deter-

Table II. ESR Parameters and (K^+_{free}) for Added Concentrations of $KClO_3$ Added to the Anion Radical of 2,6-Di-*tert*-butylbenzoquinone in HMPA

($KClO_3$)$_{total}$[a]	$1/(A^\circ - \bar{A})$, G^{-1}	(K^+_{free})	(K^+)$_{metal}$[b]	K_a
0.05085	12.209	0.02927	0.00059	26.7
0.05328	12.043	0.02983	0.00098	29.4
0.05252	11.938	0.03019	0.00095	27.2

[a] All concentrations are given in *M*. [b] (K^+)$_{metal}$ is the contribution to the total concentration of potassium due to the potassium metal used to reduce the quinone.

mined. The concentration of the potassium ion free of ion pairing (K^+_{free}) can be calculated from this coupling constant. Since the difference between the total added salt concentration and (K^+_{free}) is the concentration of the diamagnetic ion pair, K_a for this new salt can be calculated. The anion radical concentration (about 10^{-5} *M*) is small compared to the concentration of added salt, so there is no need to account for the reduction in (K^+_{free}) due to ion pairing with the anion radical.

The addition of 0.0493 *M* KI to the anion radical solution of 2,6-di-*tert*-butylbenzoquinone in HMPA results in an observed coupling constant of 2.246 G. By the use of eq 3, (K^+_{free}) is found to be 0.0422 *M*. This corresponds to a value for K_a of 4.0. The very small value for K_a of KI necessarily leads to a large error in K_a, since (K^+, I^-) must be determined from a small difference between two large numbers. From 12 independent measurements, each from a different sample of anion radical, K_a for KI was found to 4.3 ± 1.9. This standard deviation, while large, is small in comparison with conductivity measurements. Salts with very low K_a's cannot even be determined by conductivity.

Potassium chlorate was studied in the same manner. Table II shows a representative set of data leading to a value for K_a of 27.7 ± 2.5.

Brusset and coworkers[8] have concluded from their curve of conductivity vs. concentration that KI is not fully dissociated in HMPA. However, they were not able to obtain K_a. The work presented here describes a new method for the determination of ion association constants and the only method that can be used effectively in highly solvating media such as HMPA.

It should be mentioned that the technique described here has been applied to the potassium ion only, due to the fact that conductivity data are scarce for other cations. However, there is no reason why, with future measurements, this technique could not be expanded to include other cations and other solvent systems. For systems with very small K_a's, large errors are generated due to the fact that the ion pair concentration is found from a small difference between two large numbers. For systems with very large K_a's, high concentrations of the salt must be added to the solution to generate enough free cation to interact with the 2,6-di-*tert*-butylsemiquinone. Concentrations higher than about 0.4 *M* are undesirable due to their effect upon the bulk properties of the solvent. For these reasons the technique described here is limited to the study of salts with K_a's more or less between 3 and 200. Finally it should be mentioned that the concentrations of free ions are necessarily small, and rough calculations indicate that ionic strength changes are not a significant factor. A more detailed analysis of the effects of activity coefficients and saturation factors will appear in a future publication.

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A Synthesis of Optically Active Avenaciolide from D-Glucose. The Correct Stereochemistry of the Natural Product

Sir:

Carbohydrates and their derivatives possess several attributes which make them ideal precursors for certain target molecules in synthetic organic chemistry. Four of the more obvious attributes are (i) enantiomeric purity, (ii) the high conformational bias usually displayed which results in reactions having a high degree of stereoselectivity, (iii) the ready assignment of stereochemistry by means of NMR methods which have been honed to a remarkable degree of sophistication for the analysis of carbohydrate derivatives,[1] and (iv) the intensive assembly of functional groups which can be selectively utilized through employment of appropriate protecting groups.

A consequence of attributes (i) and (ii) is the possibility to incorporate the absolute configuration of the target molecule into the synthetic planning. This general approach is particularly advantageous in the synthesis of chiral, biologically active substances, since usually only one enantiomer is effective owing to the enantioselectivity of chemoreceptors in nature.[2] Furthermore with many of these substances, the absolute stereochemistry cannot be determined directly, and derivatization or chemical transformation to known chiral products is fraught with danger. As a case in point, and in exemplification of the above-described attributes, we outline herein a synthesis[3] of optically active avenaciolide[4] (**1**) from D-glucose by a route which establishes the correct chirality of the naturally occuring enantiomer.[5]

Relationships immediately apparent between "diacetone glucose" (**2**)[6] and avenaciolide (**1**) are (a) the presence in **2** of two of the three asymmetric centers in **1** at the proper oxidation level, (b) the presence in **2** of one of the potential lactones of **1** in the guise of the protected anomeric center, (c) the free hydroxyl group as a site for elaboration of the acetic acid unit of **1**, and (d) the 5,6-acetonide which offers ready access to the *n*-octyl group.

Objectives (c) and (d) had in fact been already realized by Rosenthal and Nguyen[7] in the conversion of **2** to the aldehyde **3**.

The conversion of **3** to avenaciolide is outlined in Scheme I. In view of the ease with which 4-aldehydo ribofuranosides epimerize,[8] it was necessary to ensure that the compound obtained in the Wittig reaction of **3** ($C_7H_{15}P^+Ph_3Br^-$, THF, BuLi, room temperature, 70%) was indeed **4** (Anal. ($C_{18}H_{30}O_5$) C, H). Had such an epimerization occurred the