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Kinetics of Complexation of Potassium Ions with Dibenzo-18-Crown-6 in Methanol by ^{39}K Nuclear Magnetic Resonance

Sir

Synthetic and naturally occurring macrocyclic ionophores, which are capable of forming stable complexes with alkali ions, have recently gained much interest.[1] Such compounds often increase the solubility of electrolytes in hydrophobic media and are thought to play a major role in the process of ion transport in biological membranes. It is therefore of interest to study the kinetics of the complexation reaction between ionophores and cations. Such studies have been performed by chemical relaxation methods, ultrasonic absorption,[2] and by ^{1}H and ^{23}Na nmr spectroscopy.[3,4]

Despite the great importance of potassium binding processes, especially in biological systems, very little use has been made of ^{39}K nmr in their study.[5] This is due to the small gyromagnetic ratio of the ^{39}K nucleus and thus its low nmr sensitivity. To overcome this limitation we have employed a superconducting magnet operating at 60 kG (corresponding to ^{39}K nmr frequency of about 12 MHz) and used it to study the complexation of potassium ions with dibenzo-18-crown-6 (DBC) in methanol. For the nmr measurements we used a pulse spectrometer equipped with a variable temperature probe. The ^{39}K signals were still quite weak, and excessive signal averaging was needed.

For the kinetics studies, the longitudinal relaxation times (T_1) of ^{39}K were measured in methanol solutions containing 0.48 M KI and 0.14 M DBC over a wide range of temperatures. The results of these measurements are presented in Figure 1. Also shown are results for a methanol solution containing 0.5 M KI but no DBC. Comparison of the two sets of data clearly indicates the occurrence of a kinetic process in which potassium ions exchange back and forth between the solvated and complexed form according to eq 1.

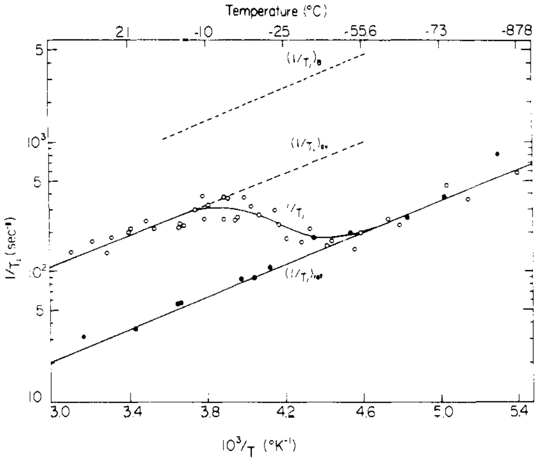

Figure 1. Semilog plots of $1/T_1$ of ^{39}K in a methanol solution *vs.* reciprocal absolute temperatures. The open circles correspond to a solution containing 0.48 M KI and 0.14 M DBC, while the closed circles correspond to a solution containing 0.5 M KI but no DBC. The continuous curves for the DBC solution were calculated using the parameters given in the text. Measurements were done at 12 MHz (60 kG).

$$\mathrm{K^+ + DBC} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{(K^+, DBC)} \qquad (1)$$

The interpretation of the results presented in Figure 1 is similar to that given previously for the ^{23}Na case.[4a] It is based on quadrupole relaxation effects of ^{39}K (I = $3/2$) in the two environments under consideration. In the solvated form, the nmr relaxation rate of ^{39}K is relatively long, due to the more symmetric structure of this form, while in the (K$^+$, DBC) complex the symmetry around the K$^+$ ion is considerably reduced, and at the same time the correlation time is increased, resulting in fast nuclear relaxation. In the low temperature region of Figure 1 (below −55°) the exchange reaction between the two forms (eq 1) is slow, and only the signal of the solvated K$^+$ ions is observed; the free induction decay signal of the (K$^+$, DBC) complex is too fast to detect. On the other hand, in the high temperature region (above −10°) the exchange is fast and the observed relaxation rate is the average of the rates in both environments. In the intermediate region (−55 to −10°) the exchange rate is of the order of the relaxation rates, and by a quantitative analysis of the nmr data in this region kinetic parameters can be derived. The actual derivation of the kinetic parameters was done as described in detail before,[4a] and the following results were obtained: k_{-1} = 610 sec^{-1} (at −34°), ΔE = 12.6 kcal/mol. The curve in Figure 1 for the solution containing DBC was calculated on the basis of these results and the assumption of nearly complete complexation.

Similar measurements were also performed on rubidium ions in methanol solutions of RbCNS (0.64 M) and DBC (0.11 M) using ^{87}Rb nmr, (employing a 14-kG magnet which corresponds to 19.5 MHz). In these experiments the transverse relaxation rate of ^{87}Rb was measured from the free induction decay signal following a 90° pulse. The results are shown in Figure 2 together with measurements on a RbCNS solution not containing DBC. Clearly, in this case the exchange rate between the solvated and complexed form is sufficiently fast to average out the nmr signal in the two environments even at −50°. This gives a lower limit of 10^4 sec^{-1} for k_{-1} at this temperature.

The above results for potassium binding to DBC are similar to those found previously[4a] for Na$^+$ (k_{-1} = 800 sec^{-1},

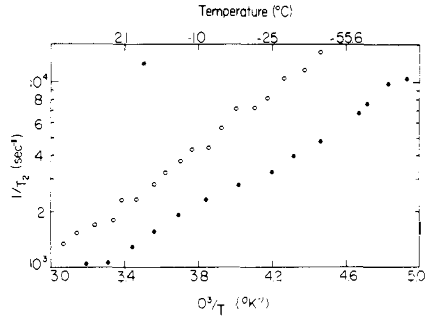

Figure 2. Semilog plots of $1/T_2$ of ^{87}Rb in methanol solutions of RbCNS *vs.* reciprocal absolute temperature. The measurements correspond to 19.5 MHz (14 kG). The open circles are for a solution containing 0.64 *M* RbCNS and 0.11 *M* DBC, while the closed circles correspond to a solution containing 0.7 *M* RbCNS but no DBC.

at −13°, and ΔE = 11.7 kcal/mol) but are considerably different from those for rubidium, for which the exchange rate is much faster. This behavior is consistent with the known structure of the corresponding complexes in the solid state as determined by X-ray crystallography.[6] These studies show that both Na^+ and K^+ fit nicely into the cavity of the crown form of DBC, while the much larger rubidium ion sticks out from it and consequently is probably less tightly bound to the DBC molecule.

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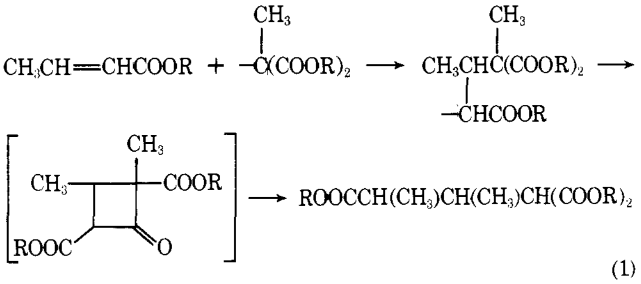
Mechanism of the Abnormal Michael Reaction between Ethyl Cyanoacetate and 3-Methyl-2-cyclohexenone

Sir:

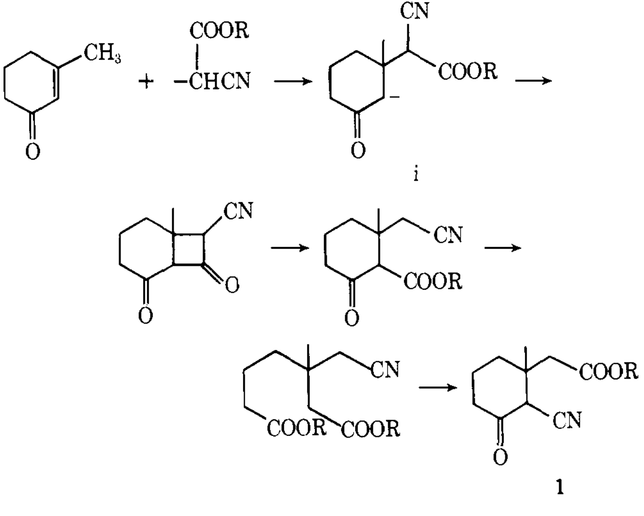
The incursion of an abnormal pathway into the normal base-catalyzed Michael addition of acyclic acceptors, frequent with monosubstituted malonates or cyanoacetates,[1] is attributed to cyclization of the initial adduct to a cyclobutanone intermediate followed by base cleavage in the opposite direction, allowing equilibration to the more acidic abnormal product; an example[2] is shown in eq 1. This mechanism, proposed early by Holden and Lapworth,[3] has been substantiated by ^{14}C and ^{18}O tracer studies.[4]



(1)

There are also reports of abnormal Michael products, particularly from cyclohexenones, which cannot be explained by the Holden-Lapworth mechanism alone. Johnson and coworkers[5] proved in 1953 that the abnormal product from ethyl cyanoacetate and 3-methyl-2-cyclohexenone, prepared originally by Farmer and Ross,[6] had structure **1**, and proposed the mechanism shown in Scheme I for its formation.

Scheme I



We present here the results of a ^{13}C and ^{14}C tracer study of the formation of **1** which rule out the published mechanism[5] and establish an alternate route to abnormal Michael products from cyclohexenones.

Use of ethyl cyanoacetate-*1*-^{14}C in the Michael reaction with 3-methyl-2-cyclohexenone led to radioactive **1**. The Johnson mechanism predicts that the label should be located at the ester carbonyl; liberation of this carbon was achieved by the Barbier-Wieland degradation. As anticipated, the β-ketonitrile moiety is apparently protected from Grignard addition by enolization, so that reaction of **1** with excess phenylmagnesium bromide led to hemiketal **2**, mp 158-160°, in 77% yield. Compound **2**[7] showed hydroxyl and nitrile absorption but no carbonyl bands in the ir, and the nmr spectrum revealed two aromatic rings but only one hydroxyl. Dehydration of **2** with iodine in refluxing acetic acid gave olefin **3**,[7] mp 107-109°, which showed nitrile (2240 cm^{-1}) and ketone (1710 cm^{-1}) bands in the ir, a vinyl proton in the nmr, and a strong uv absorption at 267 nm. Ozonolysis of **3** gave benzophenone in good yield. As shown in Scheme II, the benzophenone was nonradioactive.

The location of the label was revealed by repeating the abnormal Michael reaction with methyl cyanoacetate-*1*-^{13}C, giving **1** containing 5.5% excess atom % ^{13}C. The adduct was converted to the known[5] imide **4** and thence to its ethylene ketal[7] **5**, mp 203.5-204°. Comparison of the cmr