Molecular Devices

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[1.1.1]Cryptand: A Molecular Automatic Titrator

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An artificial molecular device is a compound designed for a specific function.[1] Molecules are sometimes synthesized, characterized, and set aside, and it is only afterwards that their potential for useful applications is revealed. Moreover, a device that was initially used for a particular purpose can later be used as a different device. This is the case for [1.1.1]cryptand (4,10,15-trioxa-1,7-diazabicyclo[5.5.5]heptadecane), which behaves as a proton sponge that can capture hydrogen ions from solution equilibria in a selective, slow, and irreversible way.[2–4] It was for this reason that [1.1.1]cryptand was recently used, many years after it was initially reported, as a chemical device for variable-pH kinetic (VpHK) experiments. Use of [1.1.1]cryptand enabled the kinetic experiment of a pH sensitive reaction to be carried out while the pH was changed in a controlled way, and was thus an alternative to a physical device (an autoburette).[5] The obtained kinetic profile, which was processed using a suitable kinetic equation, gave the pH rate profile of the species studied over the alkaline range. In this context, we anticipated the possibility of using [1.1.1]cryptand in fields other than kinetics. We report herein the unprecedented use of [1.1.1]cryptand as a "molecular automatic titrator" for the determination of thermodynamic parameters. This new kind of molecular device can replace a physical titrator, and is able to carry out analytical determinations related to an acid–base reaction.

Variable parameter kinetics (VPaK)[6–15] is based on changing the value of an environmental parameter (temperature, pH, ionic strength, etc.) during a reaction that is dependent on that parameter, and processing the kinetic profile by using an equation [Eq. (1)], where the specific rate constant is a function of the parameter ($k_{obs}(Par_i)$ = dependence function, which describes the dependence on the parameter; $Par_i(t)$ = modulating function, which describes how the parameter changes with time). In the previously reported case, Equation (2) was used, where A is the absorbance, which is the analytical parameter used to follow the reaction and pH(t) is the modulating function that describes the pH change produced by [1.1.1]cryptand.

$$-\frac{dC}{dt} = k_{obs}[Par_i(t)]C \tag{1}$$

$$-\frac{dA}{dt} = k_{obs}[\mathrm{pH}(t)](A - A_\infty) \tag{2}$$

When a molecular device is used in VPaK, two homogeneously distributed chemical systems that work together in the same environment are coupled, but are connected for only a limited part to produce a programmed result. The first system reacts and changes the environmental parameter ([H^+] in this case). The reaction of the second system is influenced by that parameter and gives information for the analytical quantification of the dependence.

Many measurements carried out under different conditions of the various environmental parameters are often required in the determination of thermodynamic quantities. If analytical instruments can be used to follow the phenomenon and an automatic change of the parameter (by using a physical or a chemical device) is possible, an equation can be used to fit the experimental data in order to obtain the terms that regulate the dependence, where a dependence function and a modulating function are present. As an example, we wish to consider a spectrophotometric determination of the pK_a of an acid by carrying out a variable-pH experiment using a [1.1.1]cryptand, which acts as a molecular variable-pH device, to replace a physical automatic titrator. The mathematical model for this experiment is given by the Henderson–Hasselbalch equation [Eq. (3)] written in the form of Equation (4), where A is the absorbance of the chemical species during the titration, and A_A and A_{HA} are the absorbances of the unprotonated and protonated species, respectively. $A = A(\mathrm{pH})$ is the dependence function, which describes the dependence of A on the pH value, $\mathrm{pH} = \mathrm{pH}(t)$ is the modulating function, which describes how the pH varies with time, and K_a, the acidic equilibrium constant, is the term that regulates the dependence. The fitting of the experimental data of A versus t gives the optimized value of K_a.

$$pH = pK_a + \log\frac{A_{HA} - A}{A - A_A} \tag{3}$$

$$A = \frac{K_a A_A + 10^{-pH} A_{HA}}{10^{-pH} + K_a} \tag{4}$$

In the neutral–alkaline pH range (ca. 5–11), [1.1.1]cryptand behaves as described by Lehn, Dye, and co-workers[4] (Scheme 1). From a fast pre-equilibrium, the protonated species slowly and irreversibly evolves to an entrapped-proton species. In the neutral–alkaline pH range, when a suitable amount of an inert acid is added, [1.1.1]cryptand smoothly changes the pH of the solution through nearly two pH units over time (Figure 1). The change is always linear, with a slope of 1×10^{-4} pH units per second for the first part of the reaction, subsequently, the gradient of the curve decreases.

An experiment was carried out where phenol red, a commonly studied molecule, was titrated spectrophotometrically with [1.1.1]cryptand, which acts as a chemical device that changes the pH of the solution. The experiment was carried

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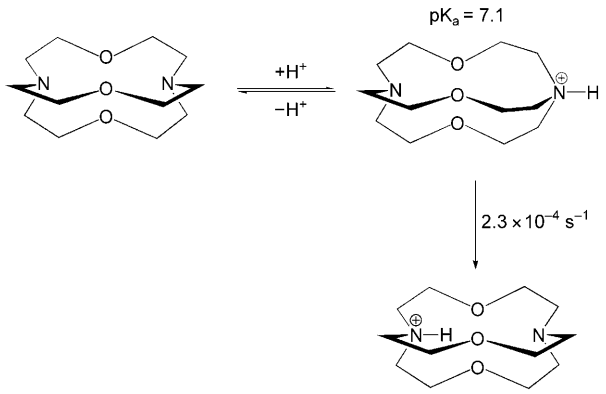

Scheme 1. Action of the [1.1.1]cyptand proton sponge in aqueous solution at 298.2 K, in the neutral–alkaline pH range.[4]

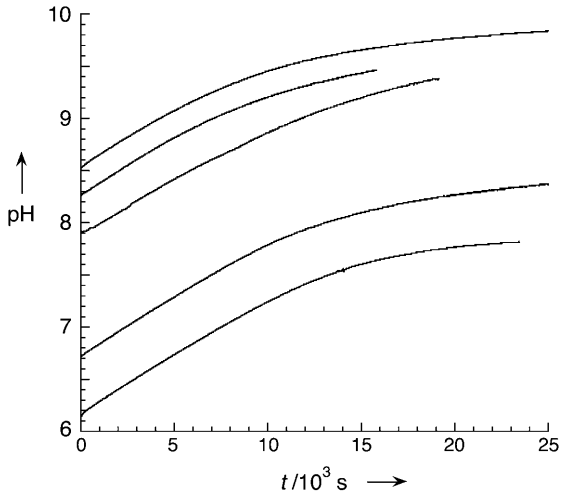

Figure 1. pH change obtained by adding suitable amounts of HBF_4 during the reaction of [1.1.1]cryptand in H_2O at 298.2 K, for different starting pH values.

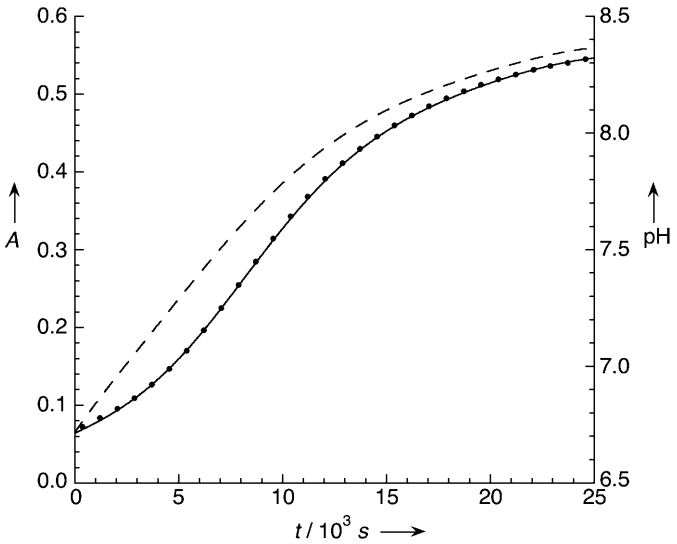

Figure 2. Absorbance change (●, selected points) during the titration of phenol red in water at 298.2 K, where the pH was changed over time (– – –) by [1.1.1]cryptand. The theoretical curve A_{calcd} derived from the mathematical model [Eq. (4)] is shown by ——.

out in a spectrophotometric cuvette thermostatted at $T=$ 298.2 K under a nitrogen atmosphere in distilled water containing [1.1.1]cryptand (ca. 0.01 M), a suitable amount of HBF_4 to give $pH_i = 6.5$, and one drop of a concentrated solution of phenol red (ca. 1×10^{-4} M in the cuvette). The ionic strength of the solution was increased by addition of KCl (0.01 M). The pH of the solution during the titration was measured by a microelectrode connected to a Metrohm 691 pH meter. The absorbance at $\lambda = 558$ nm (λ_{max} of the deprotonated phenol red species) was monitored by a Perkin–Elmer Lambda 5 spectrophotometer.

Figure 2 shows the change of both the pH and the absorbance over time during the experiment. The pH value of the solution changed in the manner described above in the range 6.5–8.5. The absorbance changed with the pH in a sigmoidal fashion as the change in absorbance of protonated and deprotonated species is regulated by the equilibrium constant at this wavelength. The fit of absorbance–time data to Equation (4) was carried out using the MicroMath SCIENTIST program[16] with a Powell-modified Marquardt algorithm[17] with K_a, A_A, and A_{HA} as the parameters to be optimized. The analytical form of the modulating function pH(t) in Equation (4) was given by a polynomial equation that describes the change of the pH value with time. The acidic constant obtained corresponds to $pK_a = 7.90 \pm 0.01$, which is in good agreement with reported values obtained under similar experimental conditions ($pK_a = 7.92$ at $I=$ 0.01 M, $T = 20\,^\circ$C).[18]

The experiment shows that the [1.1.1]cryptand works well as an automatic titrator. This technique has various advantages: 1) the use of an autoburette is eliminated; 2) there is no need to constantly change the pH of the buffer solution in the reaction vessel, thus reducing experimental time and sources of experimental errors; 3) the ionic strength remains almost constant during the experiment because ionic species are not added; 4) it is simple to use in other reaction environments that are difficult to access with physical devices (e.g., for titrations in NMR tubes); 5) it is easy to maintain an inert atmosphere; and 6) measurements are completely automatic without the need for adjustments to the external inputs.

We wish to underline some aspects of this work beyond the mere analytical applications. We previously defined a "chemical device for variable-parameter kinetic experiments" as a chemical system that is capable of changing the value of a physical parameter without influencing either the course of the main reaction studied or its instrumental monitoring.[5] Because such devices can be useful for many other experiments, we now make our definition more general and include thermodynamic determinations, as devices used in variable-parameter kinetic experiments and for variable-parameter thermodynamic determinations are different species, and are not necessarily the same. Various classes of devices, such as variable-temperature and variable-ionic strength devices, which operate at the molecular level, can be devised for other applications. [1.1.1]cryptand belongs to

both device classes as it changes the hydrogen-ion concentration, which is a very common parameter in many experimental applications, in a very efficient and discreet way. [1.1.1]cryptand is a molecular device for variable-pH experiments and is useful for VpHK determinations and for VpH thermodynamic determinations. Its performance can probably be enhanced, for example, in titrations, by shortening the time of analysis and enlarging the pH range, or by adapting the pH range for specific cases. It remains in any case an important reference model with some other interesting applications still to explore, for example, in the studies of pH-dependent unfolding of proteins[19] or in kinetics that involve pH-dependent organometallic catalysts in aqueous environments.[20] Moreover, it can be used as a part of a more complex molecular device in which its state can be kinetically controlled by means of an intermolecular proton transfer, which is similar to processes that occur in some photochemically[21] or chemically[22] activated switches.

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