

Cryptand 111: A Chemical Device for Variable-pH Kinetic Experiments

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A device is a machine or tool used for a specific task.^[1] A chemical device is a molecular species capable of performing a function at the molecular level, for example, as a drug carrier, an enzyme, or a molecular switch.^[2] During my studies aimed at developing variable-parameter kinetics^[3–13] (VPaK) I thought of exploring the possibility to use chemical systems, instead of physical ones, to change, in a known way, the value of an environmental parameter (pH, temperature, ionic strength *I*, concentration of a nucleophile *C*_{Nu}, etc.) inside a reaction vessel.

Variable-parameter kinetics enables one to obtain the dependence of the specific rate of a reaction on a physical parameter (pH, *T*, *I*, *C*_{Nu}, etc.) in a single experiment. It consists of measuring kinetics while varying the value of the parameter and fitting the obtained kinetic profiles to suitably modified kinetic equations. For a general reaction in which a species *A* reacts to give products, the mathematical model describing these experiments is given by Equation (1), where *C* is the molar concentration of species *A* and *k*_{obs} is the specific rate function of the parameter *i* varying with time. *k*_{obs}(*Par*_{*i*}) is the dependence function^[8] describing how *k*_{obs} depends on the parameter; *Par*_{*i*}(*t*) is the modulating function^[8] describing how the parameter changes with time.

$$-\frac{dC}{dt} = \left\{ k_{\text{obs}} [\text{Par}_i(t)] \right\} C \quad (1)$$

For example, in a variable-temperature kinetic (VTK) experiment carried out by applying a linear increase of temperature with time, a sigmoidal kinetic profile is usually obtained, as described by Equation (2) (integral form) where *C*₀ is the molar concentration of *A* at the start of the reaction, the dependence function is the Eyring equation,^[14] and the modulating function is *T*(*t*) = *T*₀ + *at*.

$$C = C_0 \exp \left(- \int_0^t \frac{k(T_0 + at)}{h} \exp \left(\frac{\Delta S^\ddagger}{R} \right) \exp \left(\frac{\Delta H^\ddagger}{R(T_0 + at)} \right) dt \right) \quad (2)$$

By fitting the VTK experimental data to Equation (2), the activation parameters $\Delta S^\ddagger$ and $\Delta H^\ddagger$, and then the *k*_{obs}(*T*) profile, can be obtained. For a variable-pH kinetic (VpHK)

experiment, the model is given by Equation (3), where the dependence function is given by the pH–rate profile and the modulating function describes how the pH changes with time.

$$-\frac{dC}{dt} = \left\{ k_{\text{obs}} [\text{pH}(t)] \right\} C \quad (3)$$

Several methods have been devised to produce the effects described by the modulating functions, but they always involve physical devices and external inputs to change the composition or the thermodynamic parameters of the solution (autoburettes to change the concentration of the nucleophile with time,^[3,10] pH,^[7,11] ionic strength,^[12] temperature programmers to change the temperature^[4–6,9]). To change the pH inside the reaction vessel, for example, an autoburette was used to release a concentrated solution of NaOH into a reaction environment containing 0.01M CH₃COOH, 0.01M H₃PO₄ and 0.01M H₃BO₃ to give an actual concentration of base in solution of *C*_{NaOH}(*t*)/M s^{−1} = *gM/V* (g/L s^{−1}, M/mol L^{−1} and V/L are, respectively, the release rate, the concentration of NaOH, and the reaction volume) and an almost linear increase of pH in the range 3–10.^[7]

Here I introduce for the first time the use of a chemical species as the origin of the variable-parameter conditions described by the modulating function. This approach does not require any external input to modify the solution, since the modulating-function device is present in the solution from the beginning.

Any chemical system capable of changing the value of a physical parameter without interfering with either the course of the main reaction studied or its instrumental monitoring can be useful as a chemical device playing the role of the modulating function for VPaK applications. Cryptand 111 (4,10,15-trioxa-1,7-diazabicyclo[5.5.5]heptadecane) is a good candidate as a chemical device for VpHK experiments.^[7] It was synthesized by Lehn and Cheney^[15] and kinetically characterized by Dye et al.^[16] The peculiarity of this “proton sponge” is that it abstracts the H⁺ ion in solution not in a fast and reversible way but slowly and irreversibly.

Scheme 1 shows the general behavior proposed by Dye et al. for cryptand 111 in solution. Cryptand conformer *ii* (*i* and *o* refer to the conformers in which N is directed inwards and outwards from the cage, respectively) is in fast equilibrium with a monoprotonated species (*io*⁺) and a diprotonated species (*o*⁺*o*⁺), in both of which H⁺ is coordinated outside the cage. These two species transform slowly and almost irreversibly into the species having H⁺ inside the cage (*i*⁺*i*, *i*⁺*o*⁺). This first application of cryptand 111 as a chemical device was operated in the neutral to alkaline pH range, so that the diprotonated species (*o*⁺*o*⁺, *i*⁺*o*⁺, *i*⁺*i*⁺) are not present in a

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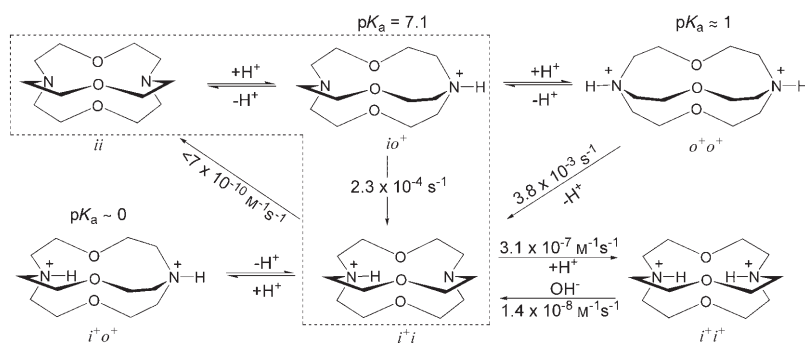
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Scheme 1. General behavior of cryptand 111 in aqueous solution at 298 K.^[15] The dashed line delimits species present in the neutral to alkaline pH range.

relevant concentration, and the scheme can be reduced to the region delimited by the dashed line. The reaction $io^+ \rightarrow ii^+$, abstracting H^+ ions from the solution equilibria, is responsible for changing the pH (the reaction $i^+i \rightarrow ii$ is several orders of magnitude slower and can be neglected).

Since cryptand 111 is a weak Brønsted base, when added to solution it is hydrolyzed according to Scheme 1 and gives an alkaline pH (for $C = 0.01\text{ M}$, pH 9.5). To use it as a VpHK device at lower pH it is necessary to move the pH to the desired initial value (pH_i) by adding a suitable amount of acid. In this way it is ready to start its slow change of pH with time in the chosen range. I performed different experiments under various conditions and tried mathematical models to describe the behavior of this molecule. Nevertheless, before examining closely these interesting aspects, I first attempted to use it as a variable-pH kinetic device.

I carried out a variable-pH kinetic experiment to determine, in a single run, the dependence on pH of the pseudo-first-order rate constant^[17] of the hydrolysis of aspirin^[18] in the alkaline pH range of 8–10, using cryptand 111 to create the variable-pH conditions. (This classic reaction model was chosen because aspirin hydrolysis has quite a complex dependence on pH and it is representative of the experimental effort usually required in the elucidation of the reaction mechanism in the pharmaceutical field, where preliminary physicochemical profiling of thousands of drug candidates can be expensive.^[19]) The experiment was carried out at 298.2 K under a nitrogen atmosphere in a sealed quartz spectrophotometric cell containing cryptand 111 (ca. 0.01 M in distilled water), HBF_4 in appropriate amount to give $pH_i \approx 8$, and acetylsalicylic acid. The pH during the reaction was measured by a microelectrode immersed inside the solution connected to a Metrohm 691 pH meter and acquired by a computer. The absorbance at 298.5 nm was monitored by a Perkin-Elmer $\lambda 5$ spectrophotometer and automatically stored in a computer.

Figure 1 shows the change in pH caused by the reaction of cryptand 111 and the change in absorbance originating from the hydrolysis of aspirin during the VpHK experiment. The pH increases almost linearly in the first part of the experiment with a gradient of 1×10^{-4} pH units per second and then increases more slowly. At the same time, the absorbance due to formation of salicylic acid increases with increasing rate, that is, the reaction is accelerated by an increase of the rate constant with increasing pH. The mathematical model

describing this process is given by Equation (4), where A and A_∞ are respectively the absorbance at time t and at the end of the reaction, and $k_{\text{obs}}[pH(t)]$ is the specific rate function of the pH changing with time.

$$-\frac{dA}{dt} = \left\{ k_{\text{obs}}[pH(t)] \right\} (A - A_\infty) \quad (4)$$

Given the mathematical form of the dependence function $k_{\text{obs}}(pH)$ and the modulating function $pH(t)$ and having an almost complete kinetic profile of the reaction, a direct fit of the experimental data ($A-t$) to

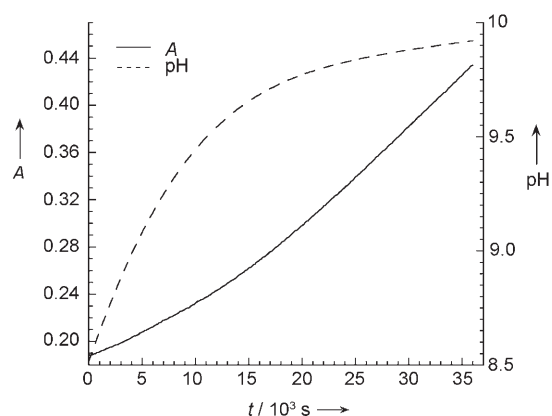


Figure 1. Change in absorbance (solid line) during the hydrolysis of aspirin at 298.2 K while the pH was changed with time (dashed line) by the chemical device cryptand 111.

Equation (4) can give the terms regulating the dependence of k_{obs} on pH. Otherwise, a differential calculation can be performed. According to Equation (4), in fact, the kinetic profile obtained by a VpHK experiment contains in each point information about the specific rate at that time and then at that pH. By dividing the derivative of the kinetic profile by $A - A_\infty$, the entire $k_{\text{obs}}(pH)$ profile can be obtained.

Figure 2 shows the dependence on pH of the specific rate of aspirin hydrolysis in the range explored, as obtained by dividing the derivative of the kinetic profile shown in Figure 1 (calculated with the Savitsky–Golay algorithm^[20]) by $A - A_\infty$. In the same figure four points are also shown for four experiments carried out under traditional constant-pH kinetics (CpHK) conditions. The results, within the experimental error, are the same but they required tens of times longer than the VpHK experiment.

This simple experiment shows that the VpHK device cryptand 111 works well. Advantages of its use are various: 1) Elimination of physical devices (e.g., autoburettes); 2) Elimination of dilution effects on adding concentrated NaOH solution. This allows a small reaction volume to be used (3 mL), savings in chemicals, and enables carrying out the reaction inside the spectrophotometer cell, so that measuring absorbance in an external reactor with an optical fiber probe can be avoided; 3) Elimination of concentration

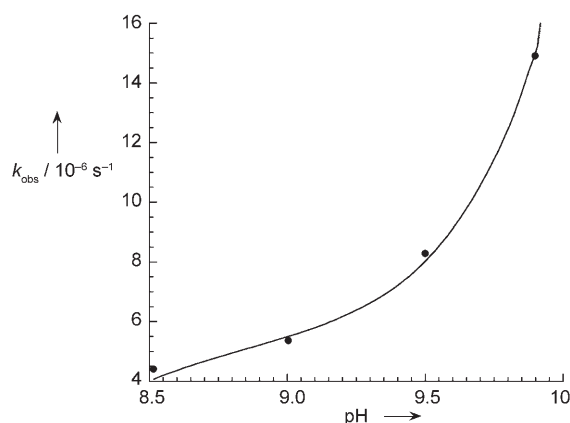


Figure 2. pH–rate profile (solid line) of the hydrolysis of aspirin in the alkaline range, as obtained by a single VpHK experiment with cryptand 111 as VpHK device. Filled circles refer to CpHK experiments.

gradients in the reaction vessel, so stirring is unnecessary; 4) Simple use of VpHK in reaction environments difficult to access by physical devices (e.g., NMR tube); 5) Ease of maintaining an inert atmosphere. All these advantages are strictly linked to the absence of the need for external input adjustments.

However, the presence of a chemical device in a variable-pH kinetic experiment also requires some specific cautions. Thus, to obtain reliable results from the kinetic profile, in addition to the care suggested for the general VpHK procedure,^[7] attention is required to the possibility of undesired reactions involving the device that can modify directly (e.g., coordination, oxidation) or indirectly (e.g., general acid–base catalysis) the course of the reaction under study.

Further work can be done to obtain, for example, a larger pH range of action or a modulation in the rate of pH change to obtain better kinetic matching with various systems. (The ideal would be a molecular system that can produce the whole pH variation required by the pH–rate profile in a time on the order of magnitude of the main reaction time. This would give the maximum information with minimum experimental error.) In this way chemical devices of this kind can become of general use for studying reaction mechanisms in organic, inorganic, and biological fields. Moreover, anywhere and for any purpose an automatic and well-described change of pH

with time is required to condition a chemical environment, devices such as cryptand 111 can be used.

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- [1] *Collins English Dictionary*, 3rd ed., HarperCollins Publishers, Glasgow, **1991**.
- [2] V. Balzani, A. Credi, M. Venturi, *Molecular Devices and Machines—A Journey into the Nano World*, Wiley-VCH, Weinheim, **2003**.
- [3] G. Alibrandi, *J. Chem. Soc. Chem. Commun.* **1994**, 23, 2709–2710.
- [4] G. Alibrandi, *Inorg. Chim. Acta* **1994**, 221, 31–34.
- [5] G. Alibrandi, M. Micali, S. Trusso, A. Villari, *J. Pharm. Sci.* **1996**, 85, 1105–1108.
- [6] R. Romeo, G. Alibrandi, *Inorg. Chem.* **1997**, 36, 4822–4830.
- [7] G. Alibrandi, S. Coppolino, N. Micali, A. Villari, *J. Pharm. Sci.* **2001**, 90, 270–274.
- [8] G. Alibrandi, S. D'Aliberti, R. Pedicini, *Chem. Educ.* **2001**, 6, 185–191.
- [9] G. Alibrandi, S. Coppolino, S. D'Aliberti, P. Ficarra, N. Micali, A. Villari, *J. Pharm. Biomed. Anal.* **2002**, 29, 1025–1029.
- [10] G. Alibrandi, S. D'Aliberti, G. Tresoldi, *Int. J. Chem. Kinet.* **2003**, 35, 497–502.
- [11] G. Alibrandi, S. Coppolino, S. D'Aliberti, P. Ficarra, N. Micali, A. Villari, *J. Pharm. Sci.* **2003**, 92, 1730–1733.
- [12] G. Alibrandi, S. Coppolino, S. D'Aliberti, R. Ficarra, N. Micali, A. Villari, *J. Pharm. Biomed. Anal.* **2003**, 32, 1073–1079.
- [13] G. Alibrandi in *Pharmaceutical Manufacturing Handbook: Regulation and Quality* (Ed.: S. C. Gad), Wiley, Hoboken, **2008**, pp. 699–722.
- [14] a) J. W. Moore, R. G. Pearson, *Kinetics and Mechanism*, Wiley, New York, **1981**; b) R. G. Wilkins, *Kinetics and Mechanism of Reactions of Transition Metal Complexes*, VCH, Weinheim, **1991**.
- [15] J. Cheney, J. M. Lehn, *J. Chem. Soc. Chem. Commun.* **1972**, 487–488.
- [16] P. B. Smith, J. L. Dye, J. Cheney, J. M. Lehn, *J. Am. Chem. Soc.* **1981**, 103, 6044–6048.
- [17] J. T. Carstensen in *Drug Stability, Principle and Practice*, 3rd ed. (Eds.: J. T. Carstensen, C. T. Rhodes), Marcel Dekker, New York, **2000**, pp. 57–111.
- [18] L. J. Edwards, *Trans. Faraday Soc.* **1950**, 46, 723–735.
- [19] a) E. H. Kerns, *J. Pharm. Sci.* **2001**, 90, 1838–1858; b) A. Avdeef, B. Testa, *Cell. Mol. Life Sci.* **2002**, 59, 1681–1689.
- [20] A. Savitzky, J. E. Golay, *Anal. Chem.* **1964**, 36, 1627–1639.