

Transition-state Acidities and the pH Dependence of Drug Stability*

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The pH dependence of hydrolytic reactions of drugs allows some control of their stability through adjustment of the pH of storage. The transition-state acidity concept of J. L. Kurz is shown to apply to the systematics of relevant pH rate profiles. As limiting cases for the hydrolysis of a series of carboxylic acid derivatives (often employed in pro-drug modifications) in neutral and basic solution, two situations are considered: 1) larger structural effects in basic solution, in which case the most stable compound of the series has the highest transition-state pK_a , and 2) larger structural effects in neutral solution, in which case the most stable compound will have the lowest transition-state pK_a . The former is the expected situation for variations of reactant electronic features because the negatively charged transition state for the hydroxide-promoted reaction in basic solution should respond more sensitively to electronic effects than should the dipolar transition state for the »uncatalyzed« reaction in neutral solution. Available data for some important substrates in fact do not show the expected behavior, which may be indicative of a concerted reaction (no tetrahedral intermediate) for reactive substrates with hydroxide ion, a mechanism for which others have already provided evidence, and possible reaction through an ion pair for the reaction of reactive substrates with water.

* This paper is dedicated to the memory of Professor Stanko Borčić, 1931–1994.

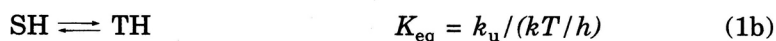
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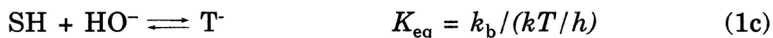
INTRODUCTION

Professor Stanko Borčić contributed greatly to our knowledge of the transition states of complex organic reactions in solution, and his publications will continue to serve not only for their fundamental scientific value but also as paradigms of the rational, precise dissection of difficult and significant questions. As a member of the Faculty of Biochemistry and Pharmacy in Zagreb, Professor Borčić would, we believe, have welcomed the attempt we describe here to make use of fundamental concepts of transition-state chemistry in approaching a practical problem of pharmaceutical science and would without doubt have advanced the solution to a far greater degree than we will have been able to do.

Many pharmaceutical products are stored in aqueous solution and their hydrolytic degradation presents a medical problem. Drug-stability studies commonly include the establishment of a profile of degradative rate data *vs.* pH since one strategy for minimizing loss of drug is to select a pH for the storage formulation at which the drug is maximally stable, *i.e.*, at which the degradation rate is minimal. Such profiles often exhibit complex features because drugs often exist in various protomeric forms, each of which may be subject to catalytic degradation with acid catalysis, with base catalysis or spontaneously («uncatalyzed reaction» or «water reaction»). For drugs without ionizable groups in the common pH range, a frequently encountered pH profile is that shown in Figure 1 (to be discussed below). In spite of the absence of ionizable groups, the profile exhibits »breaks« similar to those seen in titration curves; this raises the question, »what is titrating?»

Joseph L. Kurz answered this question in a series of very influential papers (reviewed in Kurz¹) which introduced the concept of acid-base chemistry of transition states (most properly, of activated complexes in the transition state). Kurz showed that a reaction system consisting of parallel processes for acid catalysis, uncatalyzed reaction, and base catalysis (Eqs. 1, where SH is the substrate and TH₂⁺, TH and T⁻ are transition states for the acid-catalyzed reaction [rate constant k_h], the uncatalyzed reaction [rate constant k_u], and the base-catalyzed reaction [rate constant k_b]) would change from the acid-catalyzed pathway to an uncatalyzed pathway at a pH equal to the pK_a of the transition state for acid catalysis, pK_{a1}^* , and would change from the uncatalyzed pathway to the base-catalyzed pathway at a pH equal to the pK_a of the transition state for the neutral reaction, pK_{a2}^* , (Eqs. 2, where K_w is the ion product of water):





This is illustrated in Figure 1 for a hypothetical example. The »breaks« in the profile correspond to the acid dissociation constants of transition states. The transition state for the acid-catalyzed pathway »titrates« to the transition state for the uncatalyzed pathway with a $\text{p}K_a$ of 2; the transition state for the uncatalyzed pathway »titrates« to the transition state for the base-catalyzed pathway with a $\text{p}K_a$ of 11.

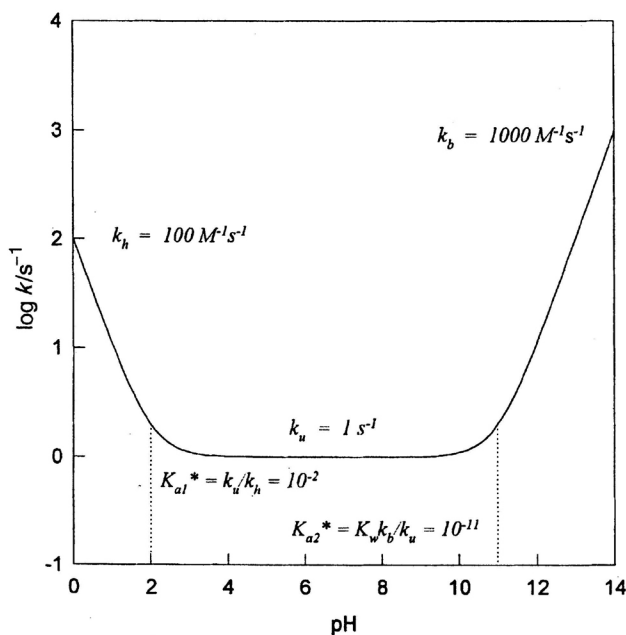


Figure 1. Schematic example of a hydrolytic pH-rate profile for a reaction exhibiting an acid-catalyzed pathway, an uncatalyzed pathway, and a base catalyzed pathway, each with the indicated rate constant.

Valuable information could be provided for drug-design purposes if a general relationship could be established between the pH-inflection points of drug-stability pH-rate profiles and structural features of drugs. As the arguments above show, such a relationship would be equivalent to a relationship between the magnitudes of transition-state acidity constants and the structures of transition states. Since the relationship between the acidities

of ordinary stable molecules and their structures is one of the best-established of chemical concepts for complex systems in solution, this could be a promising approach to the practical pharmaceutical problem.

Our purpose in this paper is to illustrate the concept by examining the results available in the literature for the transition from uncatalyzed to base-catalyzed pathways for the hydrolysis of three carboxylic-acid derivatives. This choice can be considered moderately realistic because such structures occur frequently in drugs, and are of particular importance in pro-drugs, species that have undergone potentially reversible modification to improve their physical and chemical properties for pharmaceutical use.

RESULTS AND DISCUSSION

Structure and Reactivity for the Transition from Uncatalyzed to Base-Catalyzed Reaction

Consider a series of hydrolyzable carboxylic acid derivatives such as might constitute a collection of candidate molecules for drug use. If the ratio of hydrolytic reactivities along the series is the same for the uncatalyzed reaction at neutral pH as it is for the base-catalyzed reaction at basic pH, *i.e.*, if k_b/k_u is constant for all compounds in the series, then, as Eq. 2b shows, the transition-state pK will be the same for all compounds.

On the other hand, there is no fundamental reason to expect the reactivity patterns for the two pathways to be identical. If they are not, two lim-

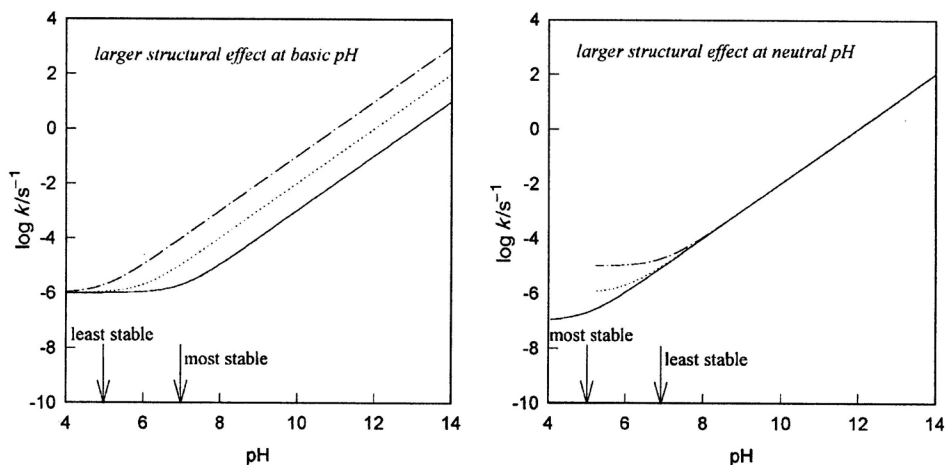


Figure 2. Schematic pH-rate profiles for a series of three compounds, each exhibiting uncatalyzed and base-catalyzed pathways of hydrolysis: two limiting cases.

iting cases arise, illustrated in Figure 2. The »break« in the profile for each compound occurs at a pH equal to the acid dissociation constant of the uncatalyzed transition state to generate the base-catalyzed transition state. Figure 2a (left) shows a case where there is little effect of substrate structure on the rate constant for the uncatalyzed reaction and a larger effect on the rate constant for the base-catalyzed reaction. In this case the least stable (most reactive) compound will have the most acidic transition state. Figure 2b (right) shows a case where there is little effect of substrate structure on the rate constant for the base-catalyzed reaction and a larger effect on the rate constant for the uncatalyzed reaction. In this case, the most stable (least reactive) compound will have the most acidic transition state. The figures also make clear that if the base-catalyzed reaction has a larger structural effect (of whatever origin), then the most stable (least reactive) compound will have the least acidic transition state ($pK_{a2} = 7$ in Figure 2a) and if the uncatalyzed reaction has the larger structural effect, then the opposite is true: the most stable compound will have the most acidic transition state ($pK_{a2} = 5$ in Figure 2b).

For derivatives of the same carboxylic acid in which electronic but not steric features of the leaving group are varied, there is reason to believe that the structural effects will be greater on the base-catalyzed reaction. As Figure 3 shows, the charge development in the transition state, which should give rise to the electronic structural effect, is dipolar in the uncatalyzed transition state but negative in the base-catalyzed transition state. In this figure, the traditional two-step mechanism through a tetrahedral interme-

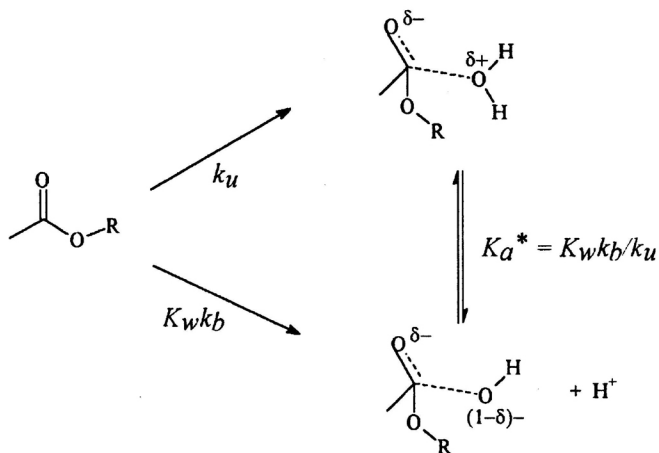


Figure 3. Hypothetical transition-state structures for the uncatalyzed hydrolysis (top, k_u) and base-catalyzed hydrolysis (bottom, $K_w k_b$) of carboxylic-acid derivatives with variable structure in the group R.

diolate is assumed and the addition step is taken to be rate-limiting. For the uncatalyzed reaction, the substituent R »sees« the development of a dipole so that variations in the electronic character of R may be expected to produce canceling energetic effects on the positive and negative poles and thus little overall effect on the rate constant. For the base-catalyzed reaction, the substituent R »sees« the development of net negative charge and this transition state should thus be stabilized by electron-withdrawal at R. The acidity constant K_a^* should therefore be largest for the substrate with the most electron-withdrawing R group, which should also be the most reactive (least stable) substrate. On this model, the expected behavior of a series of substrates is therefore that shown in Figure 2a.

In either reaction, the elimination step might also be wholly or partially rate-limiting. For the uncatalyzed transition state, this might give rise to positive charge on the leaving group and some changes in the argument, but the charge development should still be dipolar and at least some cancellation of effects should come about. For the base-catalyzed transition state, rate-limiting elimination would place negative charge directly in the leaving group and would intensify the argument given above.

The simplest prediction therefore is that the most electron-withdrawing leaving group, which will produce the least stable reactant, will give rise to the most acidic transition state (Figure 2a). This is also in accord with the elementary expectation that transition-state acidity, like reactant-state acidity, should increase with electron withdrawal.

Results for Three Derivatives

As a preliminary test of this model, we examined the data of Skrabal² for ethyl acetate and of Kirsch and Jencks³ for 2,4-dinitrophenyl acetate and acetic anhydride. The data are plotted in Figure 4. Note that the transition state pK_a is 5.1 (most acidic) for the least reactive ethyl acetate⁴, 7.3 for the more reactive 2,4-dinitrophenyl acetate, and 8.5 (least acidic) for the most reactive acetic anhydride. Thus for this series of compounds, the facts correspond to Figure 2b, in contrast to expectations on the basis of the straightforward (tetrahedral) mechanistic model just presented and shown in Figure 3. As is apparent from Figure 4, these three compounds exhibit a larger dependence of structure on reactivity for the neutral than for the basic reaction (the situation depicted in Figure 2b). Kirsch and Jencks³ have shown that the underlying structure-reactivity relationship (larger substituent effect on the uncatalyzed than on the base-catalyzed reaction) is quite general for the structural class of substituted phenyl acetates and noted that it applies to a still wider range of compounds as well. They discussed several explanations, chiefly a difference in rate-limiting step between the two pathways, but it was not possible at that time to offer a conclusive interpretation.

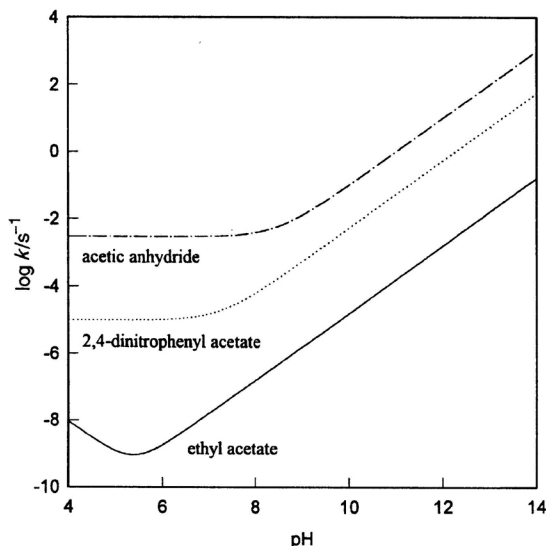


Figure 4. Experimental pH-rate profiles derived from the work of Skrabal² (ethyl acetate) and of Kirsch and Jencks³ (acetic anhydride and 2,4-dinitrophenyl acetate).

Concerted Pathways

One possible route to an explanatory model is the increasing evidence⁵⁻⁸ that fast acyl-transfer reactions (ones with strong nucleophiles and good leaving groups) may not pass through a tetrahedral intermediate but instead through a single transition state for both bond-formation to the nucleophile and bond-fission to the leaving group. This is unlikely to be true for either the base-catalyzed or the uncatalyzed reaction of ethyl acetate, but would be expected for the reaction of hydroxide ion with 2,4-dinitrophenyl acetate and with acetic anhydride. In itself, this model would not solve the problem but only make it more difficult: for the base-catalyzed reaction a concerted transition state would tend to have more charge on the leaving group than would the transition state for formation of a tetrahedral intermediate (the likely rate-limiting transition state for a two-step model of the hydroxide-ion reaction). This would make the expected substituent effect for the basic reaction still larger, while the data (Figure 4) show that the effect on the neutral reaction is dominant and produces the observed sequence of transition-state pK_a s.

Elimination-Addition Pathway Involving a Transient Ion Pair

However, a model which is consistent with the data of Figure 4 is that shown in Figure 5. This model proposes a concerted pathway for the hydro-

the transition state than in the conjugate base, results in the unusual conclusion that increasing electron withdrawal at R leads to a decrease in the acidity of the transition state.

CONCLUSION

The conclusion to be drawn from this presentation is that structure-reactivity relationships as a function of pH are not straightforward and cannot be predicted from simplistic models or generalizations. For practical applications, it will be necessary to obtain experimental data for structural effects and pH-dependence behavior for each particular system and class of compounds.

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SAŽETAK

Kiselost prijelaznog stanja stabilnosti lijekova u ovisnosti o pH

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Ovisnost hidrolitičkih reakcija lijekova o pH omogućuje kontrolu njihove stabilnosti uz ugodbu pH-vrijednosti uskladištenja. J. L. Kurzov koncept kiselosti prijelaznog stanja primijenjen je kod pH-profila brzina hidrolize. Kao granični slučajevi hidrolize u seriji derivata karboksilnih kiselina (često korištenih u modifikacijama prolijekova) u neutralnoj i lužnatoj otopini, razmotrena su dva slučaja: 1) veći struk-

turni efekti u lužnatoj otopini pri čemu najstabilniji spoj u seriji ima najviši pK_a prijelaznog stanja i 2) veći strukturni efekti u neutralnoj otopini pri čemu najstabilniji spoj u seriji ima najniži pK_a prijelaznog stanja. Pri promjenama elektronskih svojstava reaktanata prvi je slučaj očekivan, jer će negativno nabijeno prijelazno stanje u reakciji kataliziranoj hidroksidnim ionom biti više podložno elektronskim efektima nego dipolarno prijelazno stanje za »nekataliziranu« reakciju u neutralnoj otopini. Dostupni podaci za neke važne supstrate ne odgovaraju očekivanom ponašanju, već možda upućuju na usklađenu reakciju (bez tetraedarskog intermedijara) za reaktivne supstrate s hidroksidnim ionom (mehanizam koji su drugi već dokazali) i moguću reakciju preko ionskog para za reaktivne supstrate s vodom.