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MECHANISM OF GENERAL ACID CATALYSIS OF ADDITION OF AMINES TO CARBONYL GROUPS[1]

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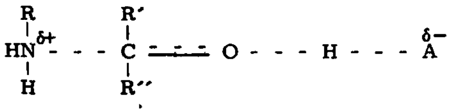
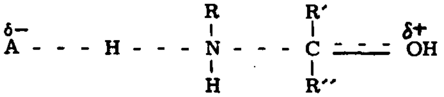
The rates of formation of oximes,[2] Schiff bases[3] and semicarbazones[4] are first order in both nitrogen compound and carbonyl compound, and exhibit general acid catalysis.

$$\mathrm{RNH_2 + R'COR'' + HA \rightleftharpoons RNHCR'R''OH + HA} \qquad (1)$$

Two likely transition states are I and II.



$$\mathrm{H\underset{\displaystyle H}{\overset{\displaystyle R}{N}}{}^{\delta+} - - - \underset{\displaystyle R''}{\overset{\displaystyle R'}{C}} \;\overset{...}{=}\; O - - - H - - - \overset{\delta-}{A}} \qquad \mathrm{I}$$

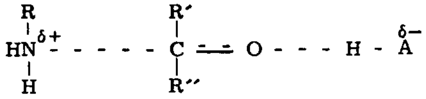


$$\mathrm{\overset{\delta-}{A} - - - H - - - \underset{\displaystyle H}{\overset{\displaystyle R}{N}} - - - \underset{\displaystyle R''}{\overset{\displaystyle R'}{C}} \;\overset{...}{=}\; \overset{\delta+}{OH}} \qquad \mathrm{II}$$

In the acid-catalyzed formation of p-nitrobenzaldehyde semicarbazone, the concentration of protonated aldehyde can be calculated from the basicity of p-nitrobenzaldehyde. The third-order rate constant for the attack of semicarbazide on this protonated species, calculated assuming the protonated aldehyde to be an intermediate, is larger than that for a diffusion-controlled reaction. Mechanism II was therefore dismissed as improbable.[4] However, this disproof is invalid. The protonated aldehyde might be only a reversibly formed by-product rather than an intermediate along the reaction path. In transition state II the protonated p-nitrobenzaldehyde is stabilized by the proximity of the amine and the anion, and therefore may be stabler than the protonated aldehyde or a transition state solvated by water alone.

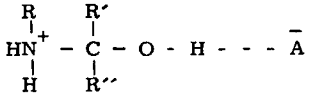
Fortunately, the "solvation rule"[5] allows an experimental distinction between these two mechanisms. It states that a proton being transferred in an organic reaction from one oxygen or nitrogen to another should lie in an entirely stable potential at the transition state and not form reacting bonds or give rise to primary hydrogen isotope effects. It should lie closer to the more basic atom (oxygen or nitrogen) at the transition state, but increasingly remote as substituents are changed to make this atom less basic.

Let us apply this rule to mechanism I. If the transition state resembles reactants, the proton in question will be located on the anion A^-, as in Ia, because A^- is more basic than the carbonyl oxygen. The slope of the Bronsted plot, α, will be less than 0.5 since the proton is then less than half transferred from its initial position on A. If the transition state resembles products, the proton will be on the alkoxide oxygen, as in Ib, and α will be greater than 0.5.



$$\underset{H}{\overset{R}{HN}}{}^{\delta+} - - - - - \underset{R''}{\overset{R'}{C}} \;\overset{-}{=}\; O - - - H - \overset{\delta-}{A}$$

Ia



$$\underset{H}{\overset{R}{HN^+}} - \underset{R''}{\overset{R'}{C}} - O - H - - - \overset{-}{A}$$

Ib

The "reacting-bond rule"[6] predicts that in a series of reactions with different nitrogen compounds, as R becomes more electron-donating, the nearest reacting bond (N–C) will become longer and the more remote reacting bond (C–O) shorter, i. e., the transition state will become more like reactants, and the carbonyl oxygen less basic. By the solvation rule, the proton should then be more remote from this oxygen but closer to A^-. In this series, for mechanism I, α should fall.

A similar analysis for mechanism II shows that α should rise. Electron-donating substituents in R will again make the transition state come earlier; this will make the nitrogen more basic. By the solvation rule, the proton should then be closer to the nitrogen and farther from A$^-$, corresponding to a rise in α.

The data in Table I show that α does fall as R becomes more electron-donating. Therefore mechanism II is incorrect. Mechanism I appears to be the simplest mechanism consistent with all data. The transition states are closer to reactants (Ia) than to products (Ib), since the Brönsted slope is less than 0.5.

TABLE I

Bronsted Slopes for Reaction 1 in Aqueous Solution at 25°[2–4]

RNH_2	$R'COR''$	pK_a of RNH_3^+	α
$NH_2NH\overset{O}{\overset{\|}{C}}NH_2$	p-ClC_6H_4CHO	3.7	0.25
"	C_6H_5CHO	"	.25
$C_6H_5NH_2$	p-ClC_6H CHO	4.6	.20[a]
NH_2OH	C_6H_5CHO	6.0	<.15[b]

[a] Calculated from data in ref. 3 for carboxylic acids only. [b] Upper limit. General acid catalysis was looked for but not observed.

It is unsafe to generalize this conclusion to include the mechanism of general acid-catalyzed addition of alcohols (rather than amines) to carbonyl groups. Examples of such reactions (or their reverse counterparts, which must have the same transition states) are hemiacetal formation, dehydration of acetaldehyde hydrate and mutarotation of glucose. The following reason leads one to expect that the mechanism of addition may change from one with A$^-$ hydrogen-bonded to the carbonyl oxonium ion, when amines add, to one with A$^-$ hydrogen-bonded to the reagent, when alcohols added. Since alcohols are much weaker bases, the reacting-bond rule requires the transition states in these hemiacetal reactions to be much closer to the carbonyl addition product. Certainly in the limit of a transition state very close to addition product, the hydrogen on the reagent alcohol (now an oxonium ion) must be more acidic than the one on the carbonyl oxygen (now an alcohol), and the base will prefer to solvate the alcoholic proton instead (as in mechanism II). Experiments on the variation of α with structure will be required to distinguish between these alternatives for the mechanism of general acid catalysis of addition of alcohols to carbonyl groups.

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