Tetrahedron Vol 24. pp 185 to 190. Pergamon Press. 1968 Printed in Great Britain

BASICITIES OF ENAMINES

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(*Received in USA* 14 *February* 1965; *accepted for publication* 11 *April* 1967)

Abstract—The possible effect of alkyl substituents on basicity of C-protonated enamines has been analyzed. It has been found that the generalization that tertiary enamines are more basic than their saturated counterparts is based on a structurally homogenous series of bases, all bearing alkyl groups at the α-position. Since α-alkyl groups exert a profound influence on basicities of pyrroles and indoles, it is proposed that the previously accepted generalizations about enamine basicities are too sweeping and should be modified in keeping with the degree and type of substitution on the double bond.

TWENTY-FIVE years ago Adams and Mahan measured the basicities of a number of cyclic enamines and concluded that as a class "vinyl tertiary amines" are more basic than the corresponding saturated compounds[1] (Table I, entries 1 and 2; 4 and 5). Later more extensive studies[2,3] strengthened the generalization and it has become widely accepted.[4,5] Some exceptions have been reported,[3] but disagreement with the generalization itself was limited[6] until the recent criticism by Stamhuis *et al.*,[7] who demonstrated that three enamines derived from isobutyraldehyde are *weaker* bases than their saturated counterparts (Table 1, entries 8 and 9).

It has since been pointed out[8] that no contradiction would exist and the conclusion of Adams and Mahan would still be valid, if it is assumed that the early workers[1-3] were measuring, as they claimed, equilibria involving C-protonated conjugate acids (Chart I, equilibrium 2), since Stamhuis, *et al.*[7] reported acidities of the N-protonated species. Unfortunately, no rigorous experimental proof of the identity of the conjugate acid(s) under the conditions of the earlier basicity measurements has ever been adduced, although it is well established that most enamines are C-protonated in the solid state.[5] The difficulty of interpreting the data is further

TABLE 1. REPORTED BASICITIES OF ENAMINES

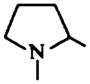
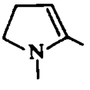
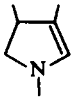
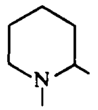
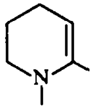
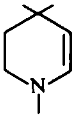
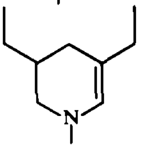
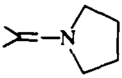
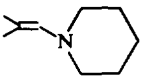
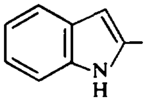
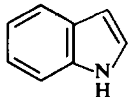
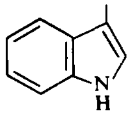
Entry	Base	p*Ka*[a]	Ref
1		10·3	1
2		11·9	1
3		9·6	10

TABLE 1—*continued*

Entry	Base	*pKa*[a]	Ref
4		10·3	1
5		11·4	1
6		10·5	*b, c*
7		9·5	10
8		8·7	7
9		8·4	7
10		−0·3[d]	9
11		−3·5[d]	9
12		−4·6[d]	9

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[a] Measured in aqueous medium at 25° unless noted otherwise.

[b] E. M. Kosower and T. S. Sorensen, *J. Org. Chem.* **27**, 3764 (1962).

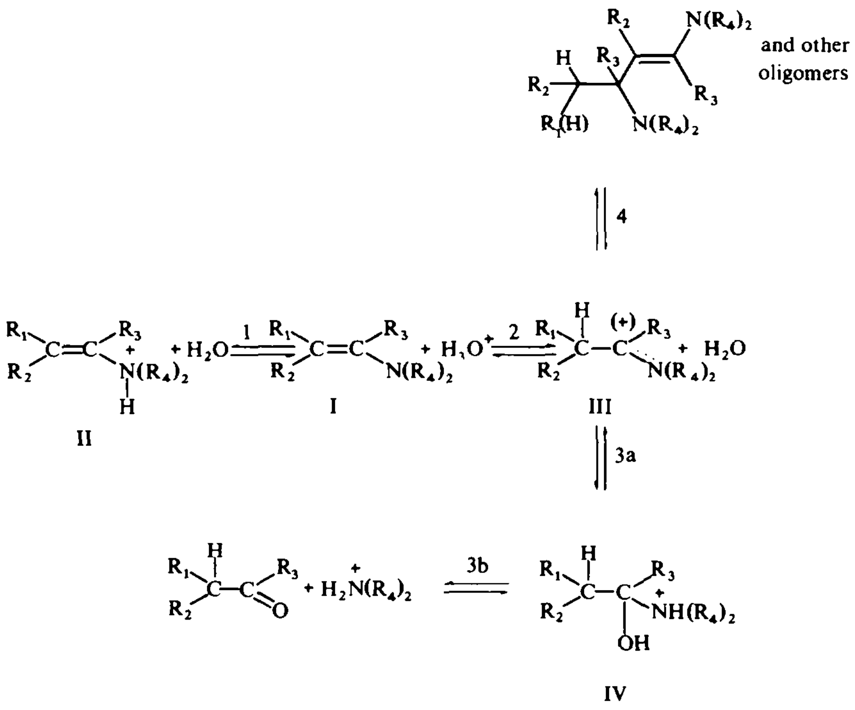
[c] The p*Ka* of a 1,4-dihydropyridine (N-vinyl enamine) was reported as 7·4 in this work. Evidence for C-protonation is derived from the UV spectrum of the conjugate acid which resembles that of an identifiably C-protonated pyrrole.[10a] However, the possibility of some N-protonation in the reduced pyridines cannot be set aside on the basis of the available evidence.

[d] Data obtained in aqueous sulfuric acid.

enhanced by the possibility of ambiguities arising from hydrolysis, as alluded to by all of the previous investigators. It is the purpose of this article, however, to show that the Adams and Mahan generalization is too sweeping, even setting aside the complicating side reactions *and assuming that only β-protonation takes place.*

A fundamental point that has passed unmentioned is the dramatic influence of structural differences on the various equilibria shown in Chart I. Changes in alkyl substitution at the α- and β-carbons of enamines will cause marked changes in stabilization of the bases and their C-protonated conjugate acids, which will be reflected in the measured basicities. Such substitution may also affect the position of protonation, the extent of polymerization, and the degree of hydrolysis.

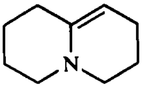
Chart I



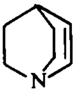
The profound effects of these structural variations on basicities have been carefully documented for indoles[9] and pyrroles,[10] which can be considered as special cases of enamines.[9] Basicities of an extensive series have been measured under conditions that permit direct observation of β-protonation uncomplicated by hydration, hydrolysis, or polymerization. A comparison of entries 10 and 11 in Table 1 illustrates a principle established with many such examples: introduction of an α-methyl group is accompanied by a basicity increase of about 3 pK units.[11] *Values of this magnitude are totally unexpected from the better-known studies of* N-*protonation of simple alkylamines,* but they are consistent with the added stabilization of the tertiary carbonium ion of an iminium salt III. Moreover, introduction of a β-alkyl group is accompanied by a *decrease* in basicity of about 1 pK unit (entries 11 and 12), ascribed[9] to the fact that an alkyl group stabilizes a double bond better than an sp^3

carbon. As suggested previously,[9] it is reasonable to assume that this structural correlation carries over to simple enamines at least in its qualitative aspect. It can then be inferred that *with respect to β-protonation enamines may be either stronger or weaker bases* than the corresponding saturated amines.

This point has not been previously recognized because the compounds most readily accessible and sufficiently stable for basicity measurements[6] have tended to be of a uniform structural type. Very few examples of enamines substituted so as to decrease carbon-basicity have been examined. In fact analysis of the structures on which the generalizations about enamine basicities are founded reveals that Adams and Mahan[1] and the majority of subsequent investigators[2, 3] surveyed almost exclusively cyclic enamines bearing an alkyl substituent at the α-position (for example, sets 1, 2 and 4, 5 of Table 1). Even compounds such as V, which in water appears to be one of the strongest known organic bases,[12] fits this structural category. From this analysis one is forced to conclude that the many reports over the past two decades of enamine basicities greater than those of saturated analogs are at least qualitatively sound, and that the results are the consequence of β-protonation coupled with the effect of α-alkyl substitution.



V



VI

The open-chain enamines studied by Stamhuis, *et al.*[7] (Table 1, entries 8, 9) presumably underwent both C- and N-protonation. Rapid hydrolysis of the C-protonated conjugate acid III prevented its buildup to observable concentrations, as shown by kinetic analysis[7] and NMR identification[8] of the components of acidified solutions of the enamines. Hence, only the equilibrium involving N-protonation was actually measured, revealing that the N-protonated enamines are weaker bases than their saturated counterparts. Unfortunately, this has little bearing on the question at hand, though it affords valuable verification of earlier studies of model compounds such as VI.[13]* However, even if it were possible to measure the equilibrium involving C-protonation, basicities less than those of the saturated amines would probably still be found, for these open-chain enamines had no alkyl group on the α-carbon but uniformly bore a methyl group at the β-position.

Although the base-strengthening effect of α-alkyl groups can be reasonably supported, the base-weakening effect of β-alkyl groups is more difficult to document, other than by consideration of the results obtained with the indole and pyrrole bases. The very few available examples of the latter effect in simple enamines are cited in Table 1 (sets 1, 2, 3 and 4, 5, 6, 7). Such results obtained with enamines which are part of 5- and 6-membered rings are probably less complicated by problems of hydrolysis (equilibria 3a and 3b) than those from linear enamines,[6, 15] though the available evidence in support of this supposition has advanced little since it was reviewed for the same purpose by Adams and Mahan.[1, 5, 6, 16]

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* The experiments reported[14] actually provide an experimentally more rigorous proof of the base-weakening effect of the vinyl group on N-protonation than do the studies of the dehydroquinuclidines since the latter, like most studies in this field, suffer from the lack of identification of species present during or even after the basicity measurements.

The fact of the base-weakening effect can be thus supported, but a variety of explanations can be advanced, in contrast to the base-strengthening effect of α-alkyl groups which is best explained by stabilization of the conjugate acid. For example, the degree of *hydration* of the iminium salt (equilibrium 3a) would be dependent on alkyl substitution. The left side of equilibrium 3a (hydration of a carbonium ion) would be more favored by the tertiary carbonium ion, as shown by the extensive studies of aryl carbinol protonation.[17] Thus a decrease in base strength with shift of an alkyl group from an α-position to a β-position could be due to the effects of alkyl substitution on the stabilization of the base and its C-protonated conjugate acid, as discussed above, and/or due to the greater tendency of the secondary carbonium ion to undergo hydration to the less basic carbinolamine.[1, 18] Entries 6 and 7 in Table 1 show two enamines which yield secondary carbonium ions on C-protonation. Since the β-substituted enamine (entry 7) is the weaker base, the effect of alkyl substitution would seem more important than carbinolamine formation. However, it is also reasonable to assume that as with indoles,[19] β-alkyl substitution would decrease the tendency for β-protonation. Thus, the decrease in basicity may also result from the intrusion of equilibrium 1, involving the N-protonated conjugate acid, even without the hydrolysis observed by Stamhuis, *et al.*[7]* These examples illustrate well the many ambiguities in explaining base-weakening effects in enamines.

In addition, one other reaction must be considered—oligomerization (equilibrium 4). This has been observed under acidic conditions with both simple cyclic enamines[3, 5, 21] and with indoles and pyrroles unsubstituted in the α-position.[22] Titration affords the maximum opportunity for such a reaction because equal concentrations of conjugate acid and free base are present at the mid-point. Again by analogy to indoles which show no tendency to dimerize when an alkyl group is present at the α-position,[22] errors from this source would be minimized in the structural series studied by Adams, although the simpler enamines which are α-blocked show more tendency to dimerize than do indoles and pyrroles.[3, 19] Iminium salts *unsubstituted* at the α-position are often converted rapidly to oligomers[3, 5, 21, 23] The oligomers bear an electron-withdrawing group near the protonated amine function, which would have a base-weakening effect.

After considering all of these factors, the high basicities of the Adams and Mahan series of enamines force one to the conclusion that C-protonated equilibria were observed but that the order of basicities reported must be restricted to the examples actually studied (α-alkyl cyclic enamine > saturated analog). Quantitative comparisons of enamine basicities and proof that a base-weakening effect of an alkyl substituent can be due to electronic effects alone must await study of enamines such as 6 and 7 under conditions that permit observation of the site of protonation, and careful experimental evaluation of the effects of alkyl substitution and ring vs. open-chain structures[16] on the extent of carbinolamine formation and overall hydrolysis. No useful study of these complex systems has yet been made.[5] Despite these unresolved problems a number of important conclusions can be drawn from the preceding analysis.

1. Alkyl substitution at either the α- or β-carbon of an enamine will profoundly

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* Leonard has shown[20] that a closely related compound is at least partly in the form of the C-protonated conjugate acid insolution. However, the actual percentage of this conjugate acid in the product mixture is unknown.

perturb the equilibria upon which the measured basicity depends. Alkyl groups at the α-position will promote β-protonation and cause marked increases in basicity by stabilization of the conjugate acid. β-Alkyl substitution will cause a decrease in base strength for one or more of the following reasons: electronic effects on the C-protonation equilibrium,[9] shift from C- to N-protonation,[7] and/or increased concentration of carbinolamine. Lack of α-substituents will result in extensive formation of oligomers which may be less basic than the simple saturated amines.

2. The greatest likelihood of measuring basicities of C-protonated enamines will be found in cyclic enamines bearing alkyl groups at the α-position. The best chance for observing β-protonation of open-chain enamines would be on those examples bearing alkyl groups at the α-position but lacking β-alkyl substitution; however, hydrolysis was rapid in closely related examples.[6]

3. Even assuming exclusive β-protonation, enamines may be either stronger or weaker bases than their saturated counterparts, as determined by substitution at the α- and β-carbon atoms.

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