Tetrahedron Letters No. 48, pp. 6057-6060, 1966. Pergamon Press Ltd.
Printed in Great Britain.

MOLECULAR ORBITAL CALCULATIONS ON QUINAZOLINES

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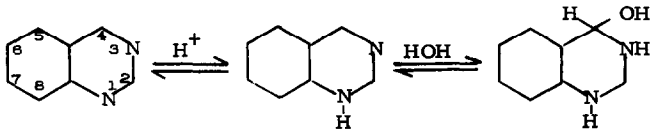
(Received 27 August 1966)

In a previous paper[1], we have demonstrated that LCAO-HMO molecular orbital calculations provide parameters which correlate with pK_{NH} values of a series of aza-analogs of 8-hydroxyquinoline. Recent work by Albert[2] and Perrin[3] and co-workers indicates that in certain nitrogen heterocyclic systems, such as quinazolines, the initial protonation is followed by rapid covalent hydration of a C-N bond. In such cases, the values of pK_{NH} obtained in the conventional manner, e.g. potentiometric titration, represent the net effect of two equilibrium processes, as shown below.



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This is of particular interest since three of the compounds treated previously[1] were substituted quinazolines, and no allowance was made for covalent hydration in carrying out molecular orbital calculations. Even though the pK_{NH} values used[1] refer to 50% aqueous dioxane, covalent hydration should be operative here as well as in 100% aqueous solutions.

Recently, values of the "True pK" relating to the position of equilibrium between structures of type I and type II have been published[4] for a series of quinazolines. We have, therefore, carried out LCAO-HMO calculations on these quinazolines in order to test the validity of the correlations observed.[1]

The procedures for calculation are summarized in the previous paper.[1] Heteroatom resonance and exchange parameters are those used previously.[1] The methoxy substituent was treated as a chain of bonded heteroatoms -O-X, and the exchange parameter[5], k, for the O-X bond was estimated by a summation process.[6] Results of these calculations are shown in Figures 1 and 2. As was shown previously[1], there is a high correlation between both

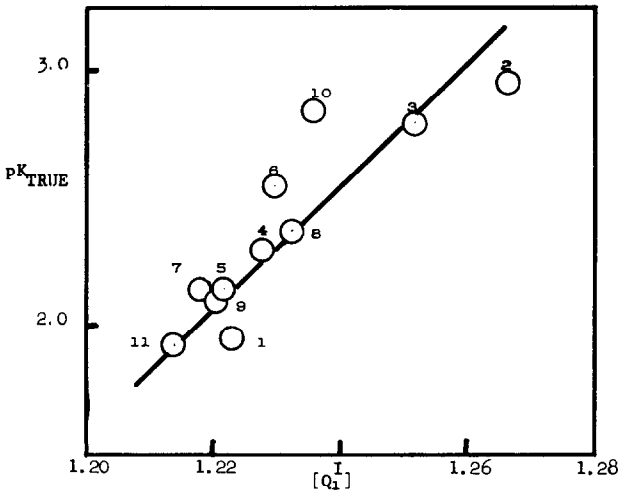

Fig. 1. Correlation of True pK_{NH} with electron density at position 1, neutral molecule $[Q_1^I]$. [1] quinazoline, [2] 2-Et, [3] 4-Me, [4] 5-Me, [5] 6-Me, [6] 7-Me, [7] 8-Me, [8] 5-OMe, [9] 6-OMe, [10] 7-OMe, [11] 8-OMe.

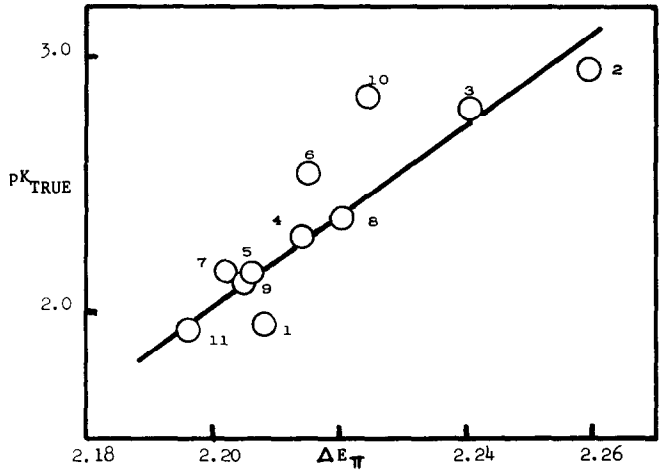

Fig. 2. Correlation of True pK_{NH} with total pi energy change, ΔE_{π}, on protonation at position 1. Refer to Fig. 1 for identification of compounds.

the π-electron energies and the electron densities at position 1 of the neutral molecules and the "true" pK_{NH} values.[4] In the present work, however, the correlation is greatly improved. The improved agreement found here is gratifying, but indicates that considerable care should be exercised in comparing experimental data with LCAO-HMO calculations, since such experimental values may in fact be a complex function of

molecular reactivity, as is true of the pK_{eqm} values of the quinazolines. Fortuitously, the quinazolines studied previously[1] are all substituted in the 4 position, so that the effect of covalent hydration is minimized[2] and $pK_{TRUE} \approx pK_{eqm}$.

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