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SUBSTITUENT EFFECTS ON AZIDO-TETRAZOLO EQUILIBRIA - s-TRIAZOLO/4,3-c/TETRAZOLO/1,5-a/PYRIMIDINES [1]

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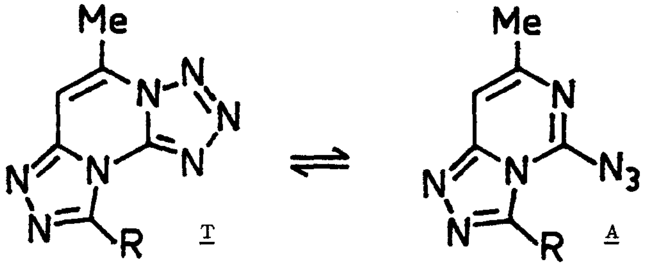
The observation of equilibria between ring-chain isomeric tetrazoloheterocycles and corresponding heterocyclic azides has stimulated extensive studies in this field.[2] The influence of a variety of heterocycles fused to the tetrazole on the equilibrium position is now well documented[2] and, in addition, solvent effects have been investigated in detail.[3] Several studies also revealed a strong influence of substituents,[4] but with the exception of at least one investigation[5] (on qualitative level) no attempts have been made to relate equilibrium constants to substituent effects.

This paper reports on a first semiquantitative correlation of substituent effects with azido-tetrazolo equilibrium constants, $K_{A/T}$,[6] in 5-aryl-9-methyl-s-triazolo/4,3-c/tetrazolo/1,5-a/pyrimidines (1-8).



1(R=4-MeOØ), 2(R=3,4-(MeO)$_2$Ø),
3(R=4-MeØ), 4(R=Ø),
5(R=4-ClØ), 6(R=4-NCØ),
7(R=3-O$_2$NØ), 8(R=4-O$_2$NØ).

In the solid state the prefered existence of 1T-8T is evidenced by the absence of any azide absorptions in the i.r. spectra in KBr or nujol. Solutions of 4 or 7 in DMSO-d_6 or DMF-d_7, examined by p.m.r. at ambient temperature, also showed the presence of only 4T and 7T. A high temperature p.m.r. study of 7 in quinoline gave no indication of a ring opening up to 410 K.

In TFA solution 1T-8T exist in equilibrium with the azides 1A-8A, even at room temperature (298 K). The equilibration is fast and completes immediately after dissolving a sample. Most probably, protonated forms of both azido and tetrazolo isomers are present in this solvent. The $K_{A/T}$ values, determined by measuring the peak areas of the well separated methyl signals of the isomers (δMe_A 2.35-2.38 ppm, $^4J_{Me,H-8}$ 0.6 Hz; δMe_T 2.74-2.80 ppm, $^4J_{Me,H-8}$ 1.1 Hz), have been found to vary with the aryl substituent.

A plot of $K_{A/T}$ vs. σ [8] gave the following simple linear equation:

$$K^{298}_{A/T}\ (\mathrm{TFA}) = 1.16_2\,\sigma + 0.40_9 \quad (\text{corr. coeff. } 0.998)$$

Thus, electron withdrawing substituents stabilize the open-chain azido isomers, and electron releasing groups favor the tetrazolo forms. Similar effects have been noted previously for some substituted tetrazolo/1,5-a/pyrimidines,[4] in agreement with general trends.[2,4] Evidently, these results support the theoretical derived key role[9] of the imino lone pair of the imidazide moiety in the formation of the new σ-bond in the transition state of the cyclization to the tetrazole, and if the validity of the principle of microscopic reversibility is supposed, this lone pair also will determine the equilibrium position. Hence, small changes of the electron density distribution caused by (relatively far removed) substituents may have a significant and definite influence on $K_{A/T}$.

Somewhat unexpected, our correlation is not of the Hammett type, i.e. log $K_{A/T}$ vs. σ, and hence it is not strictly a LFER. The plot of log $K_{A/T}$ vs. σ gives a curve similar to a logarithmic function and it is quite difficult to explain the deviation from the expected linearity. Possibly, either ΔH^o is no linear function of σ or ΔS^o varies systematic with the substituent or a combination thereof, accounting for the curvature. This could be due to steric hindrance between the azido group and the 5-aryl ring in the azido isomers and/or the different mobility (or"size") of the lone pair essential for the σ-bond formation. But, in order not to overestimate the present results, a conclusive answer is in need of the results of related studies on similar compounds. For this reason, further work on the meaning of this and related correlations is in progress.

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