Tetrahedron Letters No.19, pp. 1455-1458, 1969. Pergamon Press. Printed in Great Britain.

CONCERNING TAUTOMERIC EQUILIBRIA IN THE AZOCINE SERIES[1]

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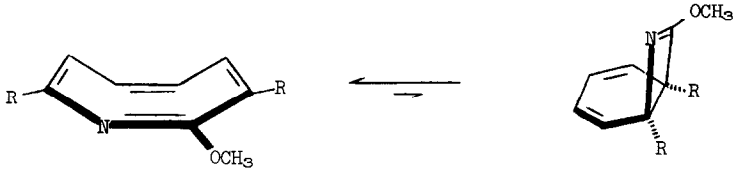
(Received in USA 1 February 1969; received in UK for publication 17 March 1969)

In a recent note, Huisgen and coworkers have summarized the existing data concerning the equilibrium position of the 1,3,5-cyclooctatriene (1) - bicyclo[4.2.0]octadiene (2) valence

1 2

tautomerism as a function of the substituents at C-7 and C-8 (cf. 1).[2] The German group has concluded that the large variation in the proportions of the monocyclic and bicyclic forms (12 derivatives have been studied) does not lend itself to ready theoretical interpretation at the present time. Independently, we have been examining the question of dynamic valence bond isomerization in nitrogen analogs of 1 and 2. Because of the obvious relationship between the two series and in view of the internal consistency of our observations, we communicate our results at this time with the intent of opening the entire question to scrutiny.

2-Methoxy-1-azocine (3a) and its 3,8-dimethyl congener 3b exhibit temperature invariant (-75 to 185°) nmr spectra which fail to provide any suggestion of the presence of bicyclic imino ethers 4a and 4b.[3] However, Diels-Alder adducts of 3a and 3b are derived exclusively

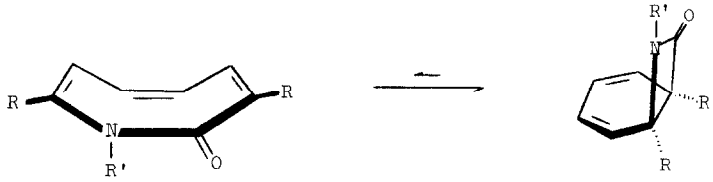


3a, R = H 4a, R = H

b, R = CH_3 b, R = CH_3

from the respective azabicyclo[4.2.0]octatrienes; furthermore, exposure of 3a to potassium t-butoxide in tetrahydrofuran solution yields benzonitrile, very probably by way of 4a.[4] The constitution and diene characteristics of 3a and 3b therefore parallel closely those of cyclooctatetraene in which the concentration of the bicyclic tautomer at 100° is only 0.01%.[5]

In marked contrast, 1,2-dihydroazocin-2-one (5a) exists predominantly as bicyclic tautomer 6a.[6] Detailed nmr studies have revealed that the concentration levels of 5a rise progressively with increasing temperature. For example, in tetrachloroethylene solution the percentage of 5a in the mixture varied as follows: 60°, 2.4%; 85°, 3.5%; 100°, 8.4%; 115°, 15.3%.

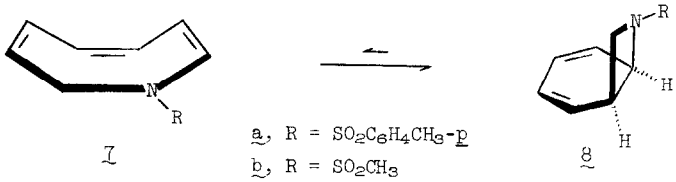


5 6

a, R = R' = H
b, R = CH_3, R' = H
c, R = R' = CH_3

Lactam 5b[6] behaved similarly. However, by comparison to 5a the percentage of monocyclic form in this instance was relatively larger and varied less with temperature: 38°, 19.5%; 95°, 20.7% (CCl_2=CCl_2 solution). Additionally, the position of equilibrium did not appear to be affected significantly by changes in solvent (all measurements at 38°): benzene-d_6, 20.3%; acetone-d_6, 20.4%; acetic acid-d_4, 22.2%.[7] The effect of a methyl group on the lactam nitrogen of 5b influences the position of equilibrium to an amazing extent. Thus, the nmr spectra of 5c[6] indicated the substance to be entirely bicyclic over a substantial temperature range (38-120°). Above 120°, 5c rapidly decomposed to o-xylene and methylisocyanate (not isolated). These data are to be contrasted with the valence tautomeric situation prevalent in cyclooctatrienone which is 93.4% monocyclic at 60°.[2]

Sulfonamides 7a[8] and 7b[6] likewise gave evidence of existing only as azabicyclooctadienes (8). Notably, therefore, replacement of the carbonyl function of a dihydroazocinone by a



7 8

a, R = $SO_2C_6H_4CH_3$-p
b, R = SO_2CH_3

methylene group and corresponding alteration in the hybridization at that position from sp^2 to sp^3 does not reverse the position of tautomeric equilibrium.

In the case of the 2-methoxy-1-azocines (3), the high equilibrium concentrations of the monocyclic forms reveal that the strain generated in passing to the bicyclic 1-azetine derivatives (4) is sufficiently large to overcome the loss of stabilization derived from non-contiguous overlap of π orbitals in 3 (because of the tub conformation). The presence of an amide function in 5a ⇋ 6a has several consequences. First, the strain in the β-lactam portion of tautomer 6 is not as great as in a 1-azetine ring; secondly, the electropositive carbon of the carbonyl group can be expected to exercise a preference for bonding to sp^3- rather than sp^2-hydridized carbon. These factors, in conjunction with the stabilization resulting from effective π overlap in the planar diene tautomer (6a), can be expected to favor 6a. The greater concentration of the monocyclic tautomer in 5b ⇋ 6b can be attributed to the eclipsed methyl-methyl interactions in 6b which are relieved in passing to 5b.

In 5c ⇋ 6c, this eclipsing interaction exists also, but apparently relief of the newly generated steric interference between N-methyl and carbonyl oxygen is overriding. The bicyclic form is heavily favored in this instance because the external bond angles in the four-membered ring are appreciably wider than those in the azocinone tautomer, thereby substantially reducing this destabilizing interaction.[9] This effect may also be important in 7 ⇋ 8 where non-bonded sulfone/methylene hydrogen interactions are involved. However, other factors such as the absence of significant strain in the azetidine ring and effective diene π-orbital overlap in 8 can be expected to stabilize 8 relative to 7.

Finally, it becomes important to reconcile the differing behavior of cyclooctatrienone and the 1,2-dihydroazocinones. Dreiding models of 5 clearly indicate that the amide linkage in the medium-sized ring is significantly distorted from planarity. This out-of-plane twisting causes reduced resonance interaction between the non-bonded nitrogen electron pair and the carbonyl π bond. In valence tautomer 6, however, the planar conformation enforced on the β-lactam ring results in restoration of total delocalization and accordant stabilization. On the other hand, cyclooctatrienone enjoys no such prerogative and the strain associated with the cyclobutanone ring in the bicyclic form is the dominant destabilizing factor.[10]

REFERENCES AND FOOTNOTES

(1) Unsaturated Heterocyclic Systems. Part LVIII.

(2) R. Huisgen, G. Boche, A. Dahmen, and W. Hechtl, Tetrahedron Letters, 5215 (1968).

(3) The nmr spectra of 3a and 3b have been described earlier.[4] The percentage composition values for 5a-6a, 7a-8a, and 7b-8b were derived from the following equation:

$$\% \text{ monocyclic} = \frac{[\text{area of vinyl absorption} - 2(\text{area of bridgehead absorption})]}{[\text{total area}]}$$

The pertinent chemical shifts are tabulated below (δ units):

	Vinyl protons	Bridgehead protons
5a-6a	5.62-6.08	3.86-4.26
7a-8a	5.48-6.04	4.58-4.85, 2.75-3.15
7b-8b	5.62-6.20	4.98-5.27, 3.05-3.55

For 5b-6b and 5c-6c, integration of the areas of the C-methyl absorptions was employed to establish the positions of equilibrium. The pertinent chemical shifts are:

	$-\overset{\vert}{\underset{\vert}{C}}-CH_3$	$=\overset{\vert}{\underset{\vert}{C}}-CH_3$
5b-6b	1.94 (broad)	1.39,1.40 (sharp)
5c-6c	----	1.24,1.28 (sharp)

(4) L. A. Paquette and T. Kakihana, J. Am. Chem. Soc., 90, 3897 (1968); see also L. A. Paquette and J. C. Philips, ibid., 90, 3898 (1968).

(5) R. Huisgen, F. Mietzsch, G. Boche, and H. Seidl, "Organic Reaction Mechanisms," Chem. Soc. Spec. Publ., 19, 3 (1965).

(6) All new compounds gave acceptable analyses and spectra, except where indicated. The syntheses of these materials will be reported in a later paper.

(7) Throughout this entire study, the solutions were allowed to equilibrate for 4-5 hr. Additionally, the spectra were rerecorded after 1 week to guard against a situation where a particularly slow rate of valence isomerization was operative.

(8) Compound 7a proved to be air-sensitive. It was characterized by its various spectra, method of synthesis, and conversion to a number of Diels-Alder adducts.[6]

(9) For pertinent examples of the change in reactivity of medium-sized ring lactams caused by N-methylation, see L. A. Paquette and L. D. Wise, J. Am. Chem. Soc., 87, 1561 (1965).

(10) We thank the National Institutes of Health and the National Science Foundation for financial support of this research.