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^{18}O STUDY OF THE MECHANISM OF FORMATION OF NITRONES AND AZOXY COMPOUNDS

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Earlier we had shown with the aid of ^{15}N that formation of azoxy compounds from aromatic nitroso compounds and aryl hydroxylamines (the so-called azoxy coupling reaction) proceeds by way of a symmetrical intermediate with chemically equivalent nitrogen atoms (1). In order to obtain additional information on the nature of this intermediate and to extend our knowledge of the mechanism of such reactions we considered it of interest to include in the studies a closely related reaction, viz., nitrone formation from aldehydes and N-substituted hydroxylamines, with the objective of elucidating the source of the oxygen atom for the products of both reactions.

Condensation of $PhNH^{18}OH$ with unlabeled nitrosobenzene gave azoxybenzene with 50% of the original ^{18}O enrichment (within the limits of experimental error) (Table 1) independent of the reaction conditions (aqueous-alcoholic alkali or aprotonic media such as benzene). On the other hand condensation of $PhNH^{18}OH$ with various aromatic aldehydes, or else condensation of $PhCH^{18}O$ with various N-substituted hydroxylamines (benzene solution in the presence of $MgSO_4$; 20°; 24 hrs.)

afforded nitrones whose ^{18}O content always corresponded to that of the hydroxylamines (Table 2).

TABLE 1

$PhNHOH + PhNO \longrightarrow PhN(O)=NPh$

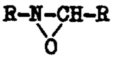
Reaction conditions	Excess ^{18}O content (at.%)		
	Phenylhydroxylamine	Nitrosobenzene	Azoxybenzene
7% Aqueous-alcoholic KOH; 2 min.; 20°	23,2	0	12,1
Benzene; 1 hr.; 80°	23,2	0	12,2

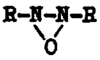
TABLE 2

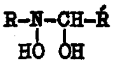
$RNHOH + R'CHO \longrightarrow RN(O)=CHR'$

R	R'	Excess ^{18}O content (at.%)		
		Hydroxylamine	Aldehyde	Nitrone
Ph	Ph	23,2	0	22,8
Ph	Ph	0	55,3	0
Ph	$p\text{-}NO_2C_6H_4$	23,2	0	23,5
$p\text{-}CH_3C_6H_4$	Ph	0	55,3	0
$p\text{-}CH_3OC_6H_4$	Ph	0	55,3	0
$PhCH_2$	Ph	0	55,3	0

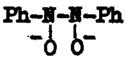
It follows from the data that hydroxylamines are 100% sources of oxygen for nitrones and only 50% sources for azoxy compounds. One may therefore exclude from consideration the possibility of the intermediate formation of three-membered heterocyclic oxaziranes (I) and oxadiaziranes (II)* through α-elimination of water elements from the arylhydroxylamine** and subsequent addition of the resultant arylazene radical to the carbonyl or nitroso group***.


(I)


(II)


$R{-}\underset{HO}{N}{-}\underset{OH}{CH}{-}R'$
(III)


$R{-}\underset{HO}{N}{-}\underset{OH}{N}{-}R$
(IV)


$Ph{-}\underset{^{-}O}{N}{-}\underset{O^{-}}{N}{-}Ph$
(V)

Naturally an ^{18}O study provided no means of proving or refuting the formation of oxadiaziranes (II) via N,N'-diols (IV) or the corresponding ions or radicals (N,N'-diols have long been regarded as intermediates in the azoxy coupling reaction). However, in the case of the reaction of hydroxylamines with aldehydes, the results obtained make it quite certain that no migration of oxygen from carbon to nitrogen occurs at any stage of the condensation. This may be considered as a quite weighty, although not direct, argument against the intermediate formation of C,N-diols (III), or of N,N'-diols (IV) which, by analogy with C,N-diols, have themselves been proposed as intermediates in the azoxy coupling

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* Although, contrary to oxaziranes (2), oxadiaziranes have as yet not been isolated, the possibility of their intermediate formation during the various isomerizations of azoxy compounds has been shown by means of ^{15}N and ^{18}O (3).

** The α-elimination of hydroxylamine ethers taking place under conditions close to those of the azoxy coupling reaction (in the presence of bases) and leading to the formation of three-membered heterocycles is well known (4).

*** Regarding the possibility of such reactions see (5).

reaction*. Indeed, had formation of C,N-diols have taken place, the subsequent elimination of water would have been at the expense of the hydroxyl attached to nitrogen rather than carbon, as the fission of a N-O bond is energetically more favorable (N-O and C-O bond energies are 61 and 75 kcal, respectively) and the rearrangement of the oxaziranes resulting from such elimination (I, R = Ar) into the final nitrones requires no additional energy (cf. 7). Moreover, the presence of a nucleophilic substituent on the nitrogen atom of diols (III) would have facilitated hydroxyl elimination from the N-atom in the formation of the oxaziranes (I). However, even here (see Table 2, R = p-tolyl, p-anisyl or benzyl) the nitrone oxygen stems exclusively from the corresponding hydroxylamine, thus disproving the oxazirane mechanism and showing the intermediate formation of C,N-diols (III) to be of little probability.

The data given in the present paper, as well as those obtained earlier with ^{15}N, are in good accord with the azoxy coupling mechanism recently proposed by Russell and Geels (8) on the basis of ESR studies. These authors concluded that in alkaline medium the symmetric intermediate has the structure of a bis-anion (V), formed from two anion radicals $PhNO^{\overline{\cdot}}$, whereas in neutral medium such a part is played by the phenyl nitroxide radical $PhNHO^{\cdot}$. It thus follows that the levelling of the isotopic composition we have observed must occur already at the stage

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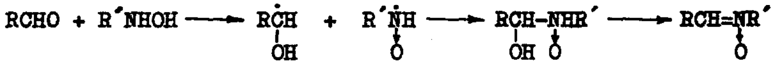
* Oae (6) obtained results similar to ours in the reaction of $PhNH^{18}OH$ with PhNO in alkaline medium, but interpreted them as evidence of the intermediate formation of the N,N'-diol (IV).

of anion-radical or radical formation.

The deep analogy between formation of azoxy compounds and nitrones, as well as the results on the nitrones obtained with the aid of ^{18}O leads to a similar mechanism for this reaction:



$$\mathrm{RCHO} + \mathrm{R'NHOH} \longrightarrow \underset{\mathrm{OH}}{\mathrm{R\dot{C}H}} + \mathrm{R'}\underset{\mathrm{O}}{\mathrm{\dot{N}H}} \longrightarrow \underset{\mathrm{OH}}{\mathrm{RCH}}\text{-}\underset{\mathrm{O}}{\mathrm{NH}}\mathrm{R'} \longrightarrow \mathrm{RCH{=}}\underset{\mathrm{O}}{\mathrm{N}}\mathrm{R'}$$

(VI) (VII)

The presence in the intermediate (VI) of a single hydroxyl (attached to carbon) makes clear the hydroxylaminic origin of the oxygen in the resulting nitrone (VII).

It should be pointed out that while the substituent species in the reactants have no bearing on the origin of the oxygen in nitrones, they have a profound effect in the azoxy coupling reaction. In the general case, as shown above, the oxygen source can be both nitroso compounds and hydroxylamines, but if the nitrogen atom in the latter is linked with a considerably more powerful nucleophilic group than in the former, the nitroso compound may turn out to be the only source of oxygen (9). This fact agreeing with the radical mechanism is of considerable importance for the synthesis of mixed azoxy compounds.

The ^{18}O content of the compounds was determined mass spectrometrically from the relative peak intensities of the ^{16}O and ^{18}O containing molecular ions, for which the authors wish to express their grateful acknowledgment to Prof. N. S. Wulfsoń and Dr. V. A. Puchkov.

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