Reactions of N-hydroxyureas and N-hydroxysulfonamides with tert-butyldisulfynyl chloride. A mechanistic and ESR spectroscopic investigation.
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Aims of the Present Research

It was in the early twenties that Whalen and Jones\(^1\) reported the reaction between an arylsulfinyl chloride and hydroxylamine. Instead of the expected N-hydroxysulfinamide the arylsulfonamide was isolated in high yield, see Scheme 1.1. The authors proposed that the sulfonamide was formed by intramolecular oxidation of the intermediate N-hydroxysulfinamide.

Since that time, several interesting reactions of N-hydroxy compounds with sulfinyl chlorides have been investigated. A survey will be given in Section 1.2. One of the most important aims of the research that will be described here is to obtain more mechanistic insight into these reactions and to study the scope of the rearrangements involved in these processes. Our work is not restricted to N-hydroxy compounds only. The corresponding reaction of a hydroperoxide was also investigated because of its structural resemblance with hydroxylamines. A hydrodisulfide, which is structurally closely related to the hydroperoxide, was also studied.

Finally, considerable attention was paid to the N-centered radicals arising as intermediates in some of these reactions. Therefore, several of the more interesting radicals (carbamoylaminals or ureyls, \(R_1R_2N-CO-N-R_3\)) were generated via independent routes starting from well-defined precursors. Many attempts were made to obtain the ESR (Electron Spin Resonance) parameters of these types of radicals.

Ureyls, like carboxamidyls \((R_1CO-N-R_2)\) have been the subject of many studies during the last decade, but have always escaped direct ESR detection in solution. In Section 1.3 a survey of the literature of the carbonylaminyl \((-CO-N-)\) radicals will be presented.
1.2 SURVEY OF THE LITERATURE OF REACTIONS OF N-HYDROXY COMPOUNDS WITH SULFINYL CHLORIDES

The report of Whalen and Jones\(^1\) was followed many years later by a number of more or less related studies. These include the reaction of \(t\)-alkylsulfinyl chlorides (RSO-Cl, \(R = t\)-butyl or 1-adamantyl) with hydroxylamines\(^2\) (RNHOH, \(R = H, n\)-butyl, cyclohexyl or \(t\)-butyl; in one case N,N-diethylhydroxylamine was used). In Chapter 5 this reaction will be discussed in more detail. Furthermore, the reaction of \(t\)-butylsulfinyl chloride with N-hydroxycarbamates\(^3\), RN(OH)CO₂R' (\(R = H, m\)ethyl and \(R' = ethyl or methyl\)) was investigated and a likely mechanism was proposed. More details are given in Chapter 3.

During the course of our work, Hudson and co-workers\(^4\) published the results of the reaction of methyl- or arylsulfinyl chlorides with oximes. These authors succeeded in isolating an intermediate product in the overall process, i.e., an O-sulfinyl oxime. The thermally induced homolytic rearrangement of this compound was accompanied by CIDNP effects (see Section 1.4) providing evidence for a radical cage process. In Scheme 1.2 the proposed mechanism is presented.

\[
\begin{align*}
R_1R_2C=\text{N-OH} & \quad \text{ether, } -30^\circ\text{C} \quad R_1R_2C=\text{N-O-S-R} \\
\text{Et}_3\text{N} & \quad \text{25}^\circ\text{C} \\
R_1R_2C=\text{N-SR} & \quad \text{or R, H, R, =Ar}
\end{align*}
\]

Other products: ArCSN, ArCHO, ArCH=NH for \(R_1 = H, R_2 = \text{Ar}\)

Recently, Heesing\(^5\) and co-workers reported the reaction of N-benzoyl-N-phenylhydroxyamine with alkylsulfinyl chlorides (RSO-Cl, \(R = \text{methyl, n-propyl, cyclohexyl or 1-adamantyl}\)). In this case, the proposed intermediate, an O-alkylsulfinyl-N-benzoyl-N-phenylhydroxyamine, could not be isolated. In Chapter 2 this reaction will be discussed more extensively.

1.3 SURVEY OF THE LITERATURE OF AMIDYL AND RELATED RADICALS

The radicals with general structure R-CO-N-R' constitute an intriguing type of N-centered paramagnetic species\(^6\). These species have been the subject
1.1 AIMS OF THE PRESENT RESEARCH

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\[
\text{ArS-Cl} + \text{H}_2\text{N-OH (2 eq.)} \xrightarrow{\text{ether, -60}^\circ\text{C}} \text{ArSNH}_2 + \text{H}_2\text{NOH} + \text{HCl} \quad (1.1)
\]

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of many, largely theoretical, investigations; especially the question of the electronic structure (see Figure 1.1) of amidyl radicals (acylaminyls, \( R\mathrm{CO-N-R'} \), with \( R, R' = \text{alkyl or aryl} \)) has been very controversial. In a \( \pi \) structure the odd electron occupies a molecular orbital which is antisymmetric with respect to reflection in the molecular plane, whereas in a \( \sigma \) state the odd electron occupies a symmetrical orbital. In recent spectroscopic and quantum mechanical studies very strong evidence was presented that carboxamidyls possess a \( \pi \) structure. However, the discussion on the succinimidoyl radical is still continuing. The structure of the ureyl radical (carbamoylaminyl, \( \text{RN-CO-N}^{-} \)) has been the subject of many speculations, mostly based on studies in a solid matrix; none of these studies, however, has given a definite answer to the structural problem.

Many radicals of the type \(-\text{CO-N-}\) have long been recognized as intermediates in chemical reactions of N-haloamides, N-nitrosamides and other compounds. The ESR parameters of these radicals are scarcely known. For example, no ESR data are available for succinimidoyl, ureyl and carbamoyl \( (\text{R-N-CO}_2\text{R'}) \) radicals. A few ESR data are known for amidyls and N-alkoxyamidyls, \( \text{R-O-N-CO-R'} \). The amidyl radicals were generated photochemically from the parent N-chloro compounds.

In our laboratory related classes of N-centered radicals, sulfonamidyls \( (\text{RSO}_2\text{N}-\text{R'}) \) and N-alkoxysulfonamidyls \( (\text{RSO}_2\text{N-OR'}) \), have been generated from the parent N-bromo compounds. In subsequent studies they were also generated by other methods. Sulfonamidyls and N-alkoxysulfonamidyls have also been proposed as intermediates in a number of chemical reactions, including the photodecomposition of N-bromosulfonamides, and N-chlorosulfonamides, the photolysis of N-cycloalkyl-N-nitrososulfonamides, and N-cycloalkyl-N-halosulfonamides or by the persulfate oxidation of N-methoxybenzenesulfonamides.
The mechanism of the radical reactions that will be described in this thesis strongly hinges on the observation of polarized NMR spectra of the products formed during these reactions. Therefore, it is appropriate to give a short introduction of this phenomenon, called Chemically Induced Dynamic Nuclear Polarization, shortly CIDNP.

In 1967 the first examples of CIDNP effects in radical reactions were reported. Since then, many studies of these intriguing effects have appeared, not only in $^1$H-NMR spectroscopy, but also, for example, for $^2$H, $^{13}$C, $^{15}$N, $^{19}$F, $^{31}$P and $^{119}$Sn nuclei. On the basis of these early experiments, a theory for CIDNP was developed by Kaptein and Oosterhoff, Closs, Adrian and others, which was called the "radical pair theory". According to this theory, there are three basic requirements for CIDNP to occur:

i) The formation of a radical pair, in a solvent cage, either in a singlet (S) or a triplet (T) state;

ii) intersystem crossing (T-S mixing) due to the difference between the radical g factors and odd electron-nuclear hyperfine interaction, causing a disturbance of the Boltzmann distribution;

iii) relaxation processes in both the radicals and the products of the radical pair. The following table elucidates these relaxation (and some other) effects which determine whether or not CIDNP will be observed.

<table>
<thead>
<tr>
<th>Time scale</th>
<th>Process</th>
</tr>
</thead>
<tbody>
<tr>
<td>$10^{-11}-10^{-10}$ s.</td>
<td>Primary recombination</td>
</tr>
<tr>
<td>$10^{-10}-10^{-7}$ s.</td>
<td>Secondary recombination</td>
</tr>
<tr>
<td>$10^{-9}-10^{-8}$ s.</td>
<td>Intersystem crossing (S-T mixing)</td>
</tr>
<tr>
<td>$10^{-6}-10^{-5}$ s.</td>
<td>Electron-spin relaxation, $T_2$</td>
</tr>
<tr>
<td>$10^{-5}-10^{-3}$ s.</td>
<td>Nuclear-spin relaxation in the radical, $T_1^R$</td>
</tr>
<tr>
<td>1 - 20 s.</td>
<td>Nuclear-spin relaxation in the product, $T_1^P$</td>
</tr>
</tbody>
</table>

Primary recombination, i.e. recombination immediately after formation of the radical pair will, in general, not give rise to CIDNP. When the radicals of the radical pair have re-encountered after a short time we speak of secondary recombination, a process that actually causes polarization of the recombination products. Intersystem crossing induces a disturbance of the Boltzmann
distribution, resulting in the polarized NMR spectra. This $S-T_D$ mixing is dependent on the magnitude of the hyperfine coupling constant $A$. $T_2$ relaxation is an example of spin-spin relaxation in the radicals that can destroy the spin correlation of the radical pair, resulting in the absence of CIDNP effects. $T_1$ relaxation is the process whereby nuclear-spin relaxation in a component of the radical pair causes an extinction of polarization for the escape product; the solvent also plays a role in the $T_1$ process. Finally, it should be noted that the nuclear-spin relaxation in the products, $T_D$, is a slow process and therefore CIDNP can be observed during formation of these products from the radical pair.

A simplified scheme (Scheme 1.3) pictures the most relevant processes involved in free-radical cage reactions.

A qualitative expression which indicates whether enhanced absorption or emission will be observed, was developed by Kaptein. Thus, Kaptein's rule enables one to predict the sign of the polarization from the equation:

$$\Gamma_{ne} = \mu \cdot \varepsilon \cdot \Delta g \cdot A_i$$

$\Gamma_{ne}$ is the sign of the observed effect, being positive (+) for enhanced absorption ($A$) and negative (-) for emission signals ($E$). $\mu$ represents the precursor multiplicity: positive for $T$ precursors, negative for $S$ precursors. $\varepsilon$ represents the nature of the product formed, i.e. recombination ($\varepsilon = +$) or escape ($\varepsilon = -$). $\Delta g$ is the difference in radical g factor of the two "caged" radicals. For example in Scheme 1.3 for product $AX$, $\Delta g = g_A - g_B$, for product $BX$ the $\Delta g$ should be $g_B - g_A$. Finally, $A_i$ is the sign of the hyperfine coupling constant between the unpaired electron and the nucleus of the radical responsible for CIDNP. The magnitude of $A_i$ directly determines the intensity of the CIDNP ef-
fects*. In fact, the CIDNP theory is rather complicated but with the aim of the basic concepts described here, it is possible to interpret the CIDNP spectra that will be presented in this thesis.

1.5 CONTENTS OF THIS THESIS

This introduction will be followed by a discussion of the results of the reaction between several N-hydroxysulfonamides and t-butylsulfinyl chloride. During this reaction a rearrangement, involving the intermediate formation of sulfonyl and sulfonamidyl radicals, occurs. The chemical behaviour of these radicals will be discussed (Chapter 2). Upon reaction of N-hydroxyureas with t-butylsulfinyl chloride, the ureyl radicals thus formed exhibit remarkable features. The results will be discussed in Chapter 3. The chemical behaviour of ureyl radicals prompted us to carry out an ESR spectroscopic investigation of these ureyls, in the hope to determine their ESR parameters. Some urea-related radicals were investigated too. The results are given in Chapter 4. Finally, in Chapter 5 we describe the reaction between t-butyl hydroperoxide and t-butylsulfinyl chloride. An analogous reaction of t-butyl hydrodisulfide will also be discussed.

A part of the work described in this thesis has been published.

1.6 REFERENCES AND NOTES

7. a) The same problem was met for sulfonamidyl radicals; in this case convincing evidence was given that sulfonamidyls also possess a \( \pi \) structure; see references 12 and 32.

* A similar expression has been advanced to derive the sign of the polarization for the so-called multiplet effects. For reasons of simplicity this equation is not discussed here, since it is not relevant for the CIDNP effects that will be described in this thesis. For an explanation of multiplet effects, see reference 42.
37. For general reviews, see
26. The formation of an amidy radical was claimed upon photolysis of 1,4-diacyl-1,4-dimethyl-tetrazene-2 at -90°C; however, on the basis of the ESR parameters this radical appeared to be the acyl nitroxide; see P. Tordo, E. Flesia and J.M. Surzur, Tetrahedron Lett., 183 (1973).