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STEREOCHEMISTRY OF ION-PAIR RETURN. ISOMERIZATION AND RACEMIZATION OF p-CHLOROBENZHYDRYL THIOCYANATE IN ACETONITRILE.*

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Isomerization of benzhydryl thiocyanates has recently been shown to occur by way of an ionization process.[1] However, isotopic exchange experiments have shown that, to obtain isomerization, ionization is not required to reach the stage of free carbonium ions.[2] A less advanced stage of ionization appears to suffice and an ''internal'' ion-pair[3] has been suggested as the main intermediate[2]

$$R\text{-}SCN \rightleftharpoons R^{+}SCN^{-} \longrightarrow R\text{-}NCS \qquad [1]$$

The recent resolution of p-chlorobenzhydryl thiocyanate in optically pure form and its correlation with the corresponding isothiocyanate,[4] has now permitted a study of the stereochemistry of isomerization. Some significant results

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of this study are reported here together with kinetic data on the racemization and isotopic exchange reactions accompanying isomerization.

$$\text{R-SCN} \xrightarrow{k_i} \text{R-NCS}$$

$$(-)\text{R-SCN} \xrightarrow{k_{rac}} \text{dl-R-SCN}$$

$$\text{R-SCN} + \overset{*}{\text{S}}\text{CN}^- \overset{k_{ex}}{\rightleftharpoons} \text{R-(}\overset{*}{\text{S}}\text{CN)} + \text{SCN}^-$$

Table I

Racemization and isomerization of p-chlorobenzhydryl thiocyanate in acetonitrile at 70° as a function of time.

t (hr)	$\frac{[\text{RNCS}]}{[\text{RSCN}]_0}$	P_{RSCN} [a]	$\bar{P}_{RNCS}$ [b,c]	S [d]
4.5	0.325	0.64	0.43	0.52
7.0	0.46	0.50	0.38	0.51
9.0	0.545	0.41	0.37	0.53
48	0.985	0.01 [e]	0.23	0.52[f]

a) Optical purity of R-SCN relative to that of the starting material.
b) Optical purity of R-NCS formed up to time t relative to that of R-SCN at zero time.
c) The relative configuration of R-NCS is the same as that of the parent R-SCN.[4]
d) Stereospecificity. For its definition, see below.
e) Calculated.
f) Corrected for racemization of the isothiocyanate.

As the data in Table I show, thiocyanate racemizes while it isomerizes. The specific rates for isomerization and for racemization appear to be about equal : $k_i = 2.4 \times 10^{-5} \mathrm{sec}^{-1}$, $k_{rac} = 2.7 \times 10^{-5} \mathrm{sec}^{-1}$. The data show further that the optical purity of isothiocyanate, $\bar{P}_{RNCS}$, decreases with time. Two factors may concur to determine this time-dependence. These are: i) racemization of the isothiocyanate once formed; and ii) racemization of the unreacted thiocyanate.

The first of these factors appears to be of negligible importance, inasmuch as the first-order specific rate of racemization of isothiocyanate has been found to be $k_{rac}^{RNCS} = 4.8 \times 10^{-7} \mathrm{sec}^{-1}$, i.e. about 50 times smaller than either racemization or isomerization of thiocyanate. Consequently the variation of $\bar{P}_{RNCS}$ with time is essentially determined by racemization of unreacted thiocyanate.*

Under these circumstances, $\bar{P}_{RNCS}$ at a given time is a weighted average of the optical purity of the isothiocyanate formed <u>up to that time</u> (eq. [2]):

$$\bar{P}_{RNCS} = S \frac{\int_0^{[RNCS]} P_{RSCN} \, d[RNCS]}{[RNCS]} \qquad [2]$$

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* Only for experiments at very long times needs a correction to be applied allowing for racemization of isothiocyanate. This is the case for the 48-hours experiment reported in Table I.

where S is the stereospecificity of the isomerization reaction, defined as the optical purity of the isothiocyanate, P_{RNCS}, formed at any time t, relative to that of the parent thiocyanate, P_{RSCN}, <u>at the same time</u>:

$$S = \left(\frac{P_{RNCS}}{P_{RSCN}} \right)_{t = 0}$$

Since $P_{RSCN} = e^{-k_{rac}t}$ and $[RNCS] = [RSCN]_0(1 - e^{-k_i t})$ equation [2] may be readily integrated to give eq. [3].

$$\bar{P}_{RNCS} = S \frac{\frac{k_i}{k_{rac} + k_i} [1 - e^{-(k_{rac} + k_i)t}]}{1 - e^{-k_i t}} \qquad [3]$$

which allows for the stereospecificity to be evaluated from k_{rac}, k_i and $\bar{P}_{RNCS}$ at any time. The values obtained are reported in the last column of Table I and their average results S = 0.52. This value implies that of one hundred isothiocyanate molecules formed, 48 lose and 52 retain the configuration of the parent thiocyanate. That the stereospecificity is greater than zero confirms that isomerization occurs, at least in part, by way of a precursor of the free carbonium ion.[2]

The measurement of the rate of isotopic exchange occurring in the presence of labeled ionic thiocyanate provides an upper limit of the rate of formation of free carbonium ions. In acetonitrile containing $NaClO_4$, the first-order rate of exchange, k_{ex}, has been found to follow an equation of the type:

$$k_{ex} = k_1 + k_2[NaSCN]_s$$

where $[NaSCN]_s$ is the molar stoichiometric concentration of the nucleophilic salt.[5] In the absence of $NaClO_4$ a similar equation holds.[6]

From exchange data concerning variously *para*-substituted benzhydryl thiocyanates,[6a] k_1 for p-chlorobenzhydryl thiocyanate is estimated to be about $1.5 \times 10^{-6} sec^{-1}$ at 70^0 in acetonitrile.

From this value the upper limit of racemization occurring by way of free carbonium ions may be determined. This is given by:

$$\frac{k_1}{k_{rac}} \cdot \frac{k_S}{k_S + k_N}$$

Since for SCN^- reacting with p-chlorobenzhydryl cation in acetonitrile k_S/k_N is of the order of 2,[7] the fraction appears to be only about 4%. Racemization then occurs for the greatest part, 96%, by way of ion-pair intermediates.[*]

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[*] In this path *the same individual groups* originally present in the optically active substrate are present also in the racemic material. A process such as this ''in which a compound with a single asymmetric center racemizes without exchanging any of the groups attached to the asymmetric center with potential external sources of such groups'' has been termed ''isoracemization'' by Cram and Gosser.[8] The term ''ipsoracemization'' seems to us a better choice for the information it seeks to convey is that the four groups involved are the same individual groups (*ipso* = he himself) and not merely equal (*iso*) groups.

In a similar fashion, the maximum fraction of isothiocyanate formed by way of carbonium ions is given by:

$$\frac{k_1}{k_i} \cdot \frac{k_N}{k_S + k_N}$$

from which it can be evaluated at about 2%. Assuming that this fraction of the total isothiocyanate product is racemic, the stereospecificity of the isomerization occurring through precursors of free carbonium ion would give a value of 0.53. In this assumption, of one hundred ion pairs collapsing to covalent state with the N atom of SCN^-, 47 lose and 53 retain the configuration of the thiocyanate from which they originated.

This result may be compared with that obtained by Goering and coworkers[9] for oxygen equilibration and racemization of carbonyl-O^{18}-labeled p-chlorobenzhydryl p-nitrobenzoate. These workers found that oxygen equilibration resulted in 62% and 57% retention of configuration in 90% and 80% aqueous acetone respectively. However, when ionic azide was present, oxygen equilibration occurred with 100% retention.[10] This finding implies that in their system racemization occurs at a more advanced ionization stage than oxygen equilibration.

The present results for p-chlorobenzhydryl thiocyanate do not allow any speculation as to whether racemization and isomerization occur as a result of covalent return from a single or from distinct ionic intermediates. Experiments designed to establish this point are well advanced and will be shortly communicated.

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