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# Kinetic study of the reactions of *O*-alkylisoureas with OH-acidic compounds†

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ABSTRACT: Kinetic investigations on the reaction of *N*,*N*′-dicyclohexyl-*O*-(1-methylheptyl)isourea with acetic acid are described. The conversion proceeds partly through the intermediacy of a methylheptylcarbenium ion. However, in dilute solution an $S_N2$ mechanism prevails. The results are discussed in terms of the simultaneous existence of two discrete mechanisms. © 1998 John Wiley & Sons, Ltd.

KEYWORDS: *N*,*N*′-dicyclohexyl-O-(1-methylheptyl)isourea; OH-acidic compounds; acetic acid; kinetics; mechanisms

## INTRODUCTION

Much attention has recently been focused on *O*-alkylisoureas since they have proved to be excellent reagents for the alkylation of OH- and SH-acidic groups (Scheme 1) and numerous synthetic applications of these reagents have been reported.[1–6] One surprising observation, however, is that the reaction of (*S*)-(+)-*N*,*N*′-dicyclohexyl-*O*-(1-methylheptyl)isourea [(*S*)-**1**] with acetic acid in cyclohexane which leads to the inverted 1-methylheptyl acetate [(*R*)-**5**] (see Scheme 3) with 100% inversion of the configuration of the optically active octan-2-ol unit.[7–9] In the case of the reaction of (*S*)-**1** with phenol in the absence of a solvent, the inversion of configuration amounts to 99.8%.[8] Thus, both reactions proceed in a highly stereospecific manner.

At first, it was not clear whether the title reaction involved an $S_N1$ or an $S_N2$ mechanism[2,10] and thus whether it was a first- or a second-order reaction. The fact that the methylheptylcarbenium ion has been confirmed as an intermediate in both conversions with OH-acidic compounds provides strong support for an $S_N1$ mechanism.[8]

More exact investigations are described in the present paper. The possibility that several mechanisms of different molecularities can operate simultaneously is known;[11] moreover, kinetic measurements often permit the interpretation of more than one mechanism.[12]

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†Dedicated to Professor E. Vowinkel on the occasion of his 70th birthday.

## RESULTS AND DISCUSSION

When an almost 1 mol $l^{-1}$ solution of *N*,*N*′-dicyclohexyl-*O*-(1-methylheptyl)isourea (*O*-AlkIU) [(*RS*)-**1**] is mixed with anhydrous acetic acid in cyclohexane, the isourea is first protonated and the *N*,*N*′-dicyclohexyl-*O*-(1-methylheptyl)isouronium acetate (*O*-AlkIUH$^+$ AcO$^-$) [(*RS*)-**2**] is generated. This salt-like compound can be isolated in the crystalline form (Scheme 2).[8]

The addition compound (*RS*)-**2** is in equilibrium with the starting materials although the position of the equilibrium is shifted strongly to the right:

$$O\text{-AlkIU} + \text{AcOH} \rightleftharpoons O\text{-AlkIUH}^+\ \text{AcO}^- \qquad (1)$$

Upon addition of acetic acid to (*RS*)-**1** at 20°C in cyclohexane, an increase in temperature can be detected. This must be due to the heat of neutralization. If, on the other hand, it were due to heat of reaction, then the poorly soluble *N*,*N*′-dicyclohexylurea (DCU) should precipitate out, but this was not the case.[13]

Hence (*RS*)-**2** must be an ionic compound. In addition, no contact ion pair is formed at concentrations lower than 0.01 mol $l^{-1}$, as determined by osmometric molecular mass measurements.[8] Under high vacuum ($1.33 \times 10^{-3}$ mbar) the crystals of (*RS*)-**2** deliquesce, leading to the conclusion that the addition compound has been cleaved into its starting components. This behaviour also supports the absence of a covalent bond between the components.[13]

Furthermore, the $^1$H NMR spectrum of (*RS*)-**2**[8] provides more evidence in favour of the existence of ionic bonding. The chemical shifts of the NH protons of the protonated isourea demonstrate their magnetic equivalence (Scheme 2). These protons also provide the positive charge on the isourea unit.


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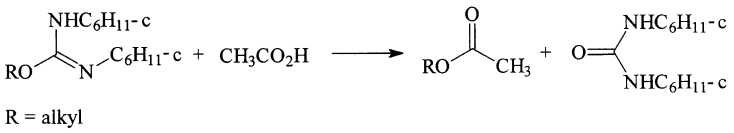
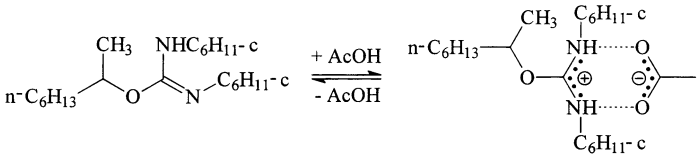



R = alkyl

**Scheme 1**




( *RS* )-**1** ( *RS* )-**2**

**Scheme 2**

At a temperature of 81.5°C the adduct decomposes irreversibly into the corresponding ester and DCU. The back reaction is impossible because the poorly soluble DCU precipitates from the reaction mixture.[8,13]

$$O\text{-AlkIUH}^{+}\ \text{AcO}^{-} \rightleftharpoons \text{AcOAlk} + \text{DCU}$$

We have now performed kinetic measurements in order to obtain more precise information about the order of the reaction.[13] For this purpose we first selected the concentration of acetic acid as a parameter and followed the effects of changes by titration. Then the results of decreasing concentrations were plotted (Figure 1) under the conditions of a first-order reaction [log $C = f(t)$].

A slightly concave curve was obtained, indicating the occurrence of a complex sequence of reactions. When the starting concentration of acetic acid was doubled, a corresponding increase in the reaction rate was not observed (Figure 2).

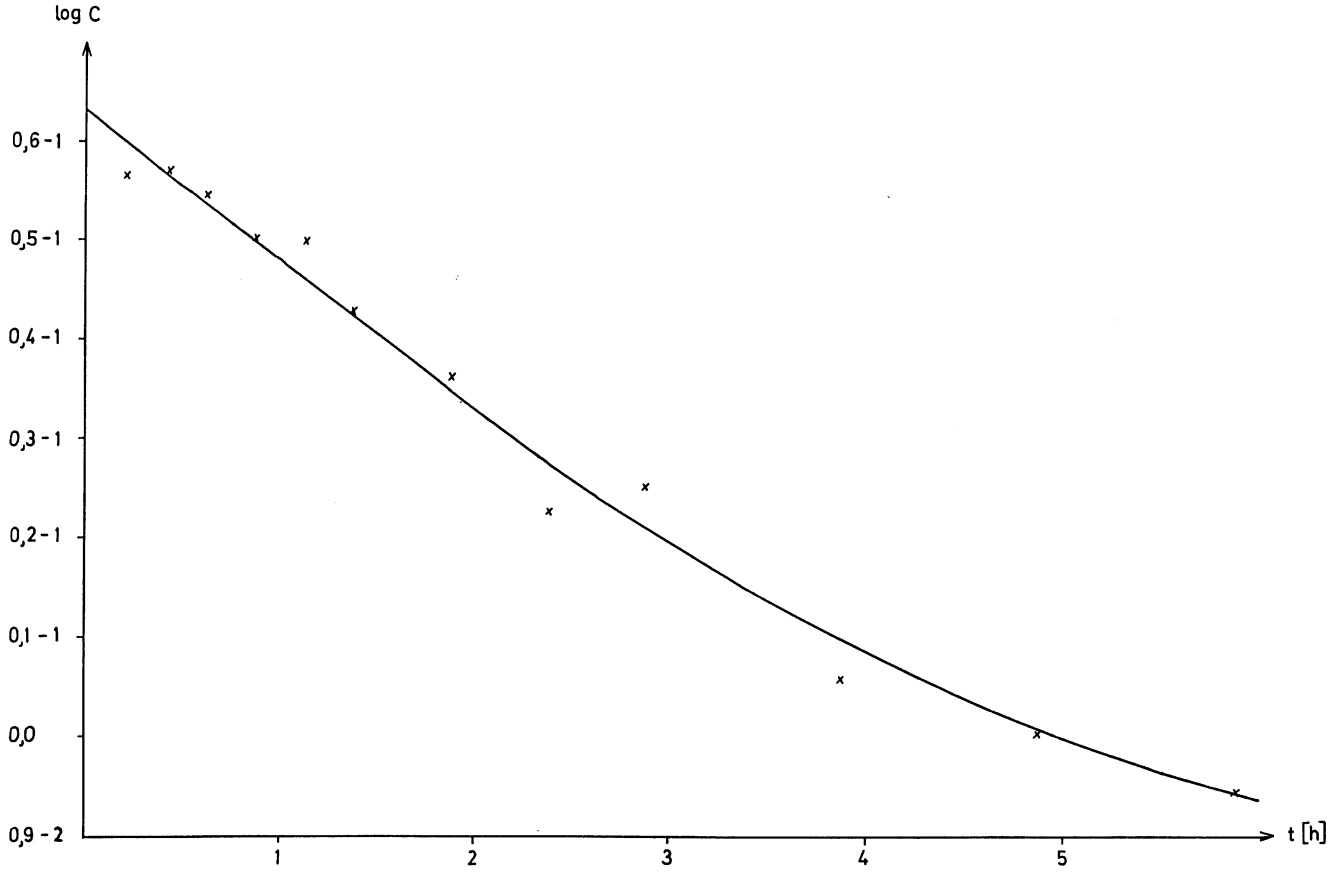



**Figure 1.** Reaction of 1 mol $l^{-1}$ *N,N'*-dicyclohexyl-*O*-(1-methylheptyl) isourea [(*RS*)-**1**; *O*-AlkIU] with acetic acid in cyclohexane

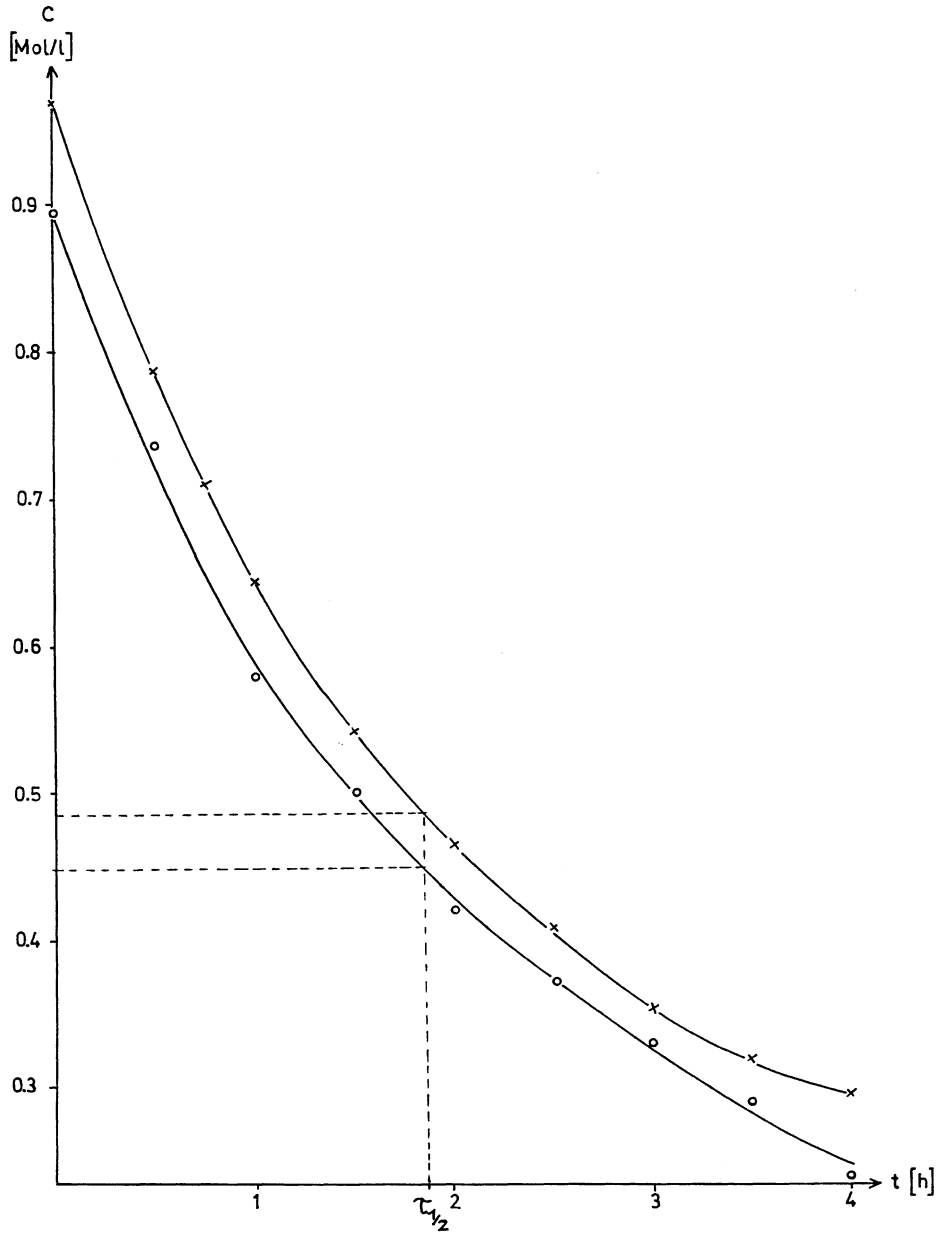



**Figure 2.** Reaction of *N,N′*-dicyclohexyl-*O*-(1-methylheptyl)isourea [(*RS*)-**1**; *O*-AlkIU], 0.895 mol $l^{-1}$ with AcOH (1:1) (o) and 0.968 mol $l^{-1}$ with AcOH (1:2) (×) in cyclohexane

This phenomenon is demonstrated by the parallel course of the curves and could be interpreted as an indication of a first-order reaction.[11,12] As expected for this reaction order, the half-lifetimes ($\tau_{1/2}$) in the initial range were independent of the concentration.[11,12] Accordingly, a first-order reaction is most likely. *N,N′*-Dicyclohexylurea was used to measure concentration changes by gravimetry. The isourea concentration values were then calculated from these results. In spite of the limitations of the gravimetric method, the reproducibility was usually at most ± 2.6% (average ± 1.3%).

If the reaction is monitored for a longer time, e.g. 12 h, and the log $C = f(t)$ plot is considered, near linearity is seen only for the first 4 h, after which the curve changes its course. These changes occur in such a way that, after the fifth hour when the isourea concentration has decreased to nearly 0.15 mol $l^{-1}$ (Figure 3 after *ca* 5 h), a change in the reaction order is apparent. A concentration–time plot appropriate for a second-order reaction [$1/C - 1/C_0 = f(t)$] supported this interpretation. After a reaction time of 5 h, this curve shows linearity, indicating that in this range the second-order rate law is valid.

Complex reaction systems of this type have been discussed elsewhere.[13] In the present case the reaction order must depend on the concentration.[11] A further aspect to be clarified was whether reaction mechanisms with differing molecularities were operative.

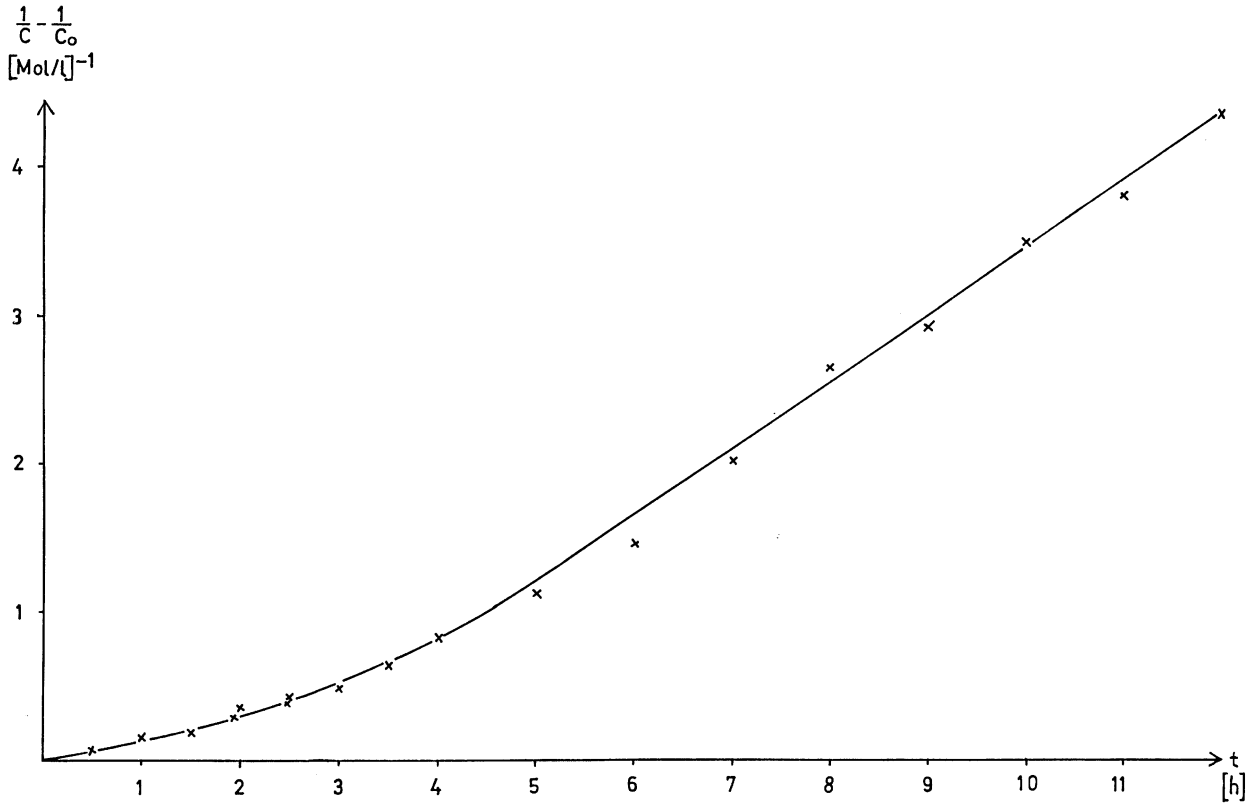



**Figure 3.** Reaction of *N,N′*-dicyclohexyl-*O*-(1-methylheptyl)isourea [(*RS*)-**1**; *O*-AlkIU] with AcOH, 0.965 mol $l^{-1}$ in cyclohexane

For the range of first-order reaction kinetics, the following mechanistic sequence of reactions can be proposed (see Figure 1):

$$O\text{-AlkIU} + \text{AcOH} \underset{k_{-1}}{\overset{k_{+1}}{\rightleftharpoons}} O\text{-AlkIUH}^+ \text{AcO}^- \quad (1)$$

$$O\text{-AlkIUH}^+ \text{AcO}^- \underset{k_{-2}}{\overset{k_{+2}}{\rightleftharpoons}} \text{OAc}^- O\text{-AlkIUH}^+ \quad (2)$$

$$\text{AcO}^- O\text{-AlkIUH}^+ \underset{k_{-3}}{\overset{k_{+3}}{\rightleftharpoons}} \text{AcO}^- \text{Alk}^+ + \text{DCU} \quad (3)$$

$$\text{AcO}^- \text{Alk}^+ \underset{k_{-4}}{\overset{k_{+4}}{\rightleftharpoons}} \text{AlkOAc} \quad (4)$$

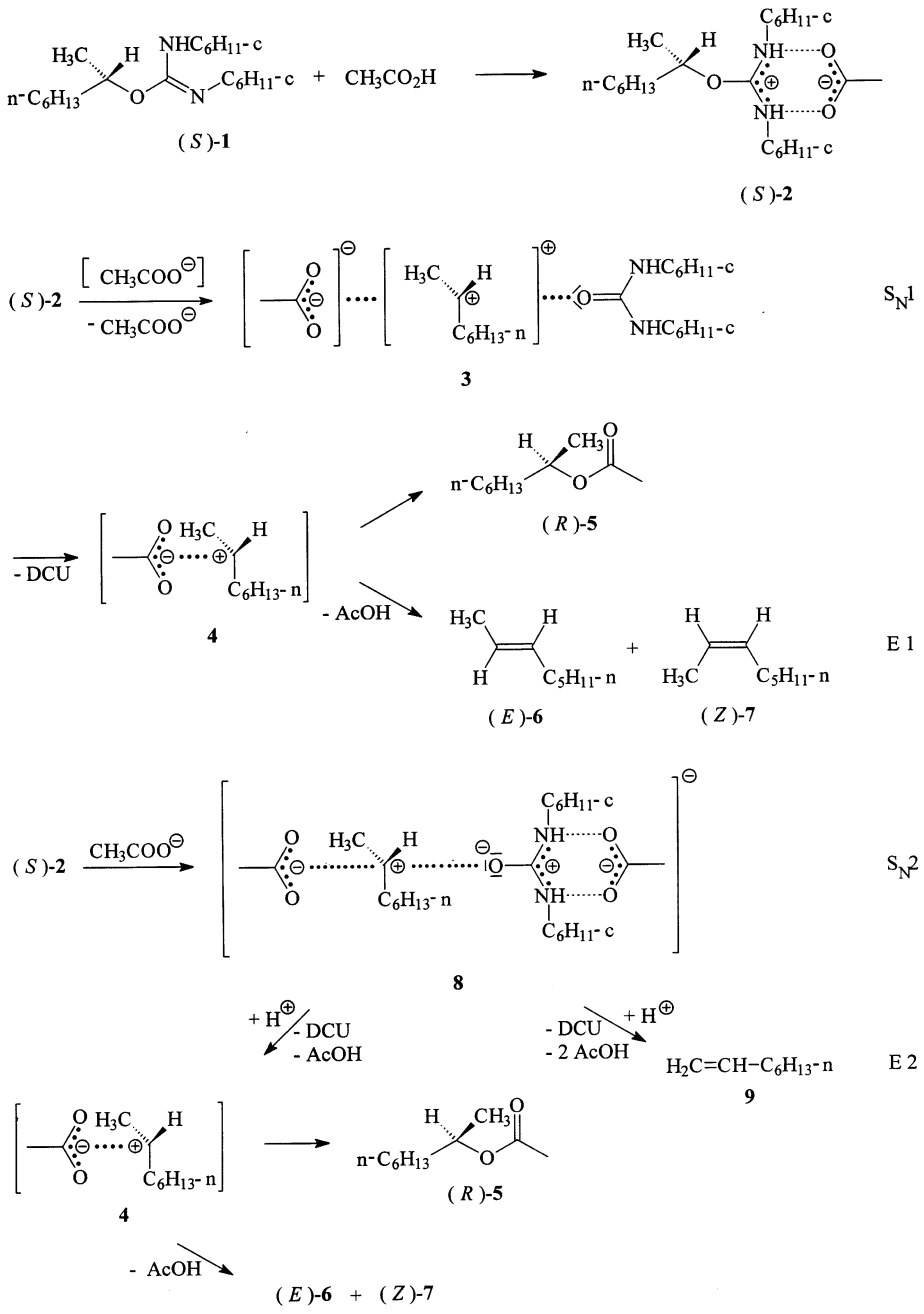
$$k_{-5} \uparrow\downarrow k_{+5} \quad (5)$$

oct-2-enes + AcOH

In the first step, *O*-AlkIUH$^+$ AcO$^-$ [(*RS*)-**2**] is formed. This addition compound then undergoes a reorientation according to equation (2) at the temperature employed, giving the species OAc$^-$*O*-AlkIUH$^+$. This ion pair subsequently reacts monomolecularly in the rate-determining step ($k_{+3}$) to furnish the ion pair AcO$^-$ Alk$^+$ (**4**), the carbocation and the acetate anion according to Sneen and co-workers.[14] It must be assumed that the acetate anion has previously become coordinatively attached to the secondary alkyl group opposite to the protonated isourea unit. Thus the first-order rate law is valid for this step. All steps except those in which DCU is formed are reversible. After the third step of the sequence, branching of the pathway occurs, one branch leading to the final product, the ester (*R*)-**5**, and the other to the elimination products, the oct-2-enes. In the latter reaction, (*E/Z*)-oct-2-enes [(*E*)-**6**; (*Z*)-**7**] are formed preferentially as the thermodynamically more stable Saytzeff products.[8] This means that the $E_1$ elimination with the carbocation **3** as intermediate predominates, a characteristic of the $S_N1$ mechanism[15] (Scheme 3).

When most of the (*RS*)-**2** has been consumed, it may be assumed that the bimolecular reaction between the isourea and the undissociated acetic acid becomes rate determining and hence that second-order kinetics prevail. Since, however, as shown by molecular mass determinations,[8] the isouronium acetate was still detectable at a low concentration of 0.02 mol $l^{-1}$, it is highly probable that at higher temperatures the rate-determining bimolecular step includes a collision between an acetate anion separated by solvent molecules and the adduct [equation (7)]. The nucleophilic attack of the acetate anion can only occur at the side of the alkyl group, i.e. from the backside (Figure 3; Scheme 3). Accordingly, at concentrations of




**Scheme 3**

less than 0.15 mol $l^{-1}$ the reaction should consequently proceed through the transition state **8** by an $S_N2$ mechanism.

The following mechanistic reaction sequence is proposed for this concentration range:

$$O\text{-AlkIU} + \text{AcOH} \underset{k_{-1}}{\overset{k_{+1}}{\rightleftharpoons}} O\text{-AlkIUH}^+\ \text{AcO}^- \qquad (1)$$

$$O\text{-AlkIUH}^+\ \text{AcO}^- \underset{k_{-2}}{\overset{k_{+2}}{\rightleftharpoons}} O\text{-AlkIUH}^+ + \text{AcO}^- \qquad (6)$$

$$\text{AcO}^- + O\text{-AlkIUH}^+\ \text{AcO}^- \underset{k_{-3}}{\overset{k_{+3}}{\rightleftharpoons}} (\text{AcO}^- \cdots O\text{-AlkIUH}^+\ \text{AcO}^-) \qquad (7)$$

$$(\text{AcO}^- \cdots O\text{-AlkIUH}^+\ \text{AcO}^-) \underset{k_{-4}}{\overset{k_{+4}}{\rightleftharpoons}} \text{AcO}^-\text{Alk}^+ + \text{DCU} + \text{AcO}^- \qquad (8)$$

$$k_{-7} \not\rightleftharpoons k_{+7} \qquad (9)$$

$$\text{oct-1-ene} + \text{AcOH} + \text{DCU} + \text{AcO}^-$$

$$AcO^- \; Alk^+ \underset{k_{-5}}{\overset{k_{+5}}{\rightleftharpoons}} \; AlkOAc \qquad (4)$$

$$k_{-6} \uparrow\downarrow \; k_{+6} \qquad (5)$$

oct-2-enes + AcOH

Here, the third, bimolecular step ($k_{+3}$), by which the transition state is formed, is rate-determining. This intermediate reacts with elimination of DCU and again forms the Sneen ion pair, the carbocation and the acetate anion. This ion pair, as already shown in the first mechanistic scheme of reactions, constitutes a branching point and leads to the ester (*R*)-**5** and the eliminations products (*E*)-**6** and (*Z*)-**7**. However, it must be assumed that the transition state **8** is the direct cause of the reaction branching leading to the by-product oct-1-ene (**9**) (Hofmann elimination) according to equation (9).[8]

Accordingly, the stereochemical result of 100% inversion of configuration with regard to the formation of the optically active ester cannot be attributed unequivocally to the second-order substitution reaction alone. Inversion occurs to the same extent in an $S_N1$ process since the methylheptylcarbenium ion is sterically shielded by the two auxiliary cyclohexylamino groups.[16]

It is well known that primary substrates react preferentially according to an $S_N2$ mechanism whereas tertiary substrates predominately react by an $S_N1$ process. The behaviour of octan-2-ol as a secondary substrate constitutes a borderline mechanism between the two limiting cases.[14a,16] Therefore, in the present case a mechanism exists that is dependent on the concentration of the substrates and can accordingly be resolved into two mechanistic schemes.[16]

During this reaction, however, the secondary alkyl cation does indeed occur as an intermediate.[8] According to Streitwieser *et al.*,[17] the cation **3** may have sufficient stability and a lifetime sufficiently long due to hyperconjugation to ensure participation of the $S_N1$ mechanism to (Scheme 3). Thus, in the present reaction, two mechanisms are possible for which, according to the concentration, the numerical values for reaction order and molecularity are identical.

With regard to the bimolecular nucleophilic substitution labelled $S_N2$, this has recently been assigned the new designation $A_ND_N$ by Guthrie.[18] In the present reaction, the attacking acetate anion approaches in an activated state along the symmetry axis and the protonated isourea departs along the same axis. Thus, the reaction coordinate is totally symmetrical along the entire pathway.

The situation is similar for the monomolecular nucleophilic substitution process $S_N1$. In Guthrie's new scheme this is designated a $D_N + A_N$ process.[18] The loss of a nucleofuge is followed in a separate step by the attack of a nucleophile (Scheme 3).

During acetolysis, the conversion of (*S*)-(+)-*N*,*N*′-dicyclohexyl-*O*-(1-methylheptyl) isourea [(*S*)-**1**] to (*R*)-(−)-1-methylheptyl acetate [(*R*)-**5**] also proceeds with a high degree of inversion (98.85%).[8] The extent of racemization is 2.3%,[8] as can be expected during solvolysis,[19] since the chance of the solvent molecules attacking the methylheptyl cation **3** nucleophilically from both sides is greater. The existence of an intermediate, nucleophilically solvated carbenium ion points to an $S_N1$-like reaction with pseudo-first-order kinetics.[12] The reaction also proceeds via an ion-pair transition state.[20]

## CONCLUSIONS

The reaction of *N*,*N*′-dicyclohexyl-*O*-(1-methylheptyl)-isourea with acetic acid has been presented as an example of a case where $S_N1$ and $S_N2$ mechanisms can operate simultaneously. Depending on the concentrations of the reactants, either first- or second-order kinetics predominate. However, this has no influence on the stereochemistry of the reaction.

## EXPERIMENTAL

*General.* IR spectra were recorded on a Perkin-Elmer model 421 spectrophotometer. Titrations were performed with a Multi-Dosimat Type E 415 system (Metrohm) and a Knick pH 35 Precision pH Meter. Molecular mass determinations were performed using a Type 301 A vapour pressure osmometer (Mechrolab).

*Materials.* AcOH was dried according to the reported procedure.[21] Cyclohexane was dried by percolation through basic $Al_2O_3$, activity I. Octan-2-ol was distilled through a packed column prior to use; GC: 4 m glass column (polyethylene glycol), 250 °C, carrier gas $N_2$, 1.4 bar; content of octan-1-ol <500 ppm and octan-3- and -4-ol, <5 ppm each; the racemic compound was resolved by the method of Vogel.[22]

*Kinetic procedures.* Kinetic measurements were carried out as follows.[13] *N*,*N*′-Dicyclohexyl-*O*-(1-methylheptyl)-isourea (30.08 g, 89.5 mmol) was weighed into a 100 ml volumetric flask and dissolved in cyclohexane (40 ml). Acetic acid (5.37 g, 89.5 mmol) was added with cooling (0 °C), the flask was filled to the mark with cyclohexane and the mixture shaken. Aliquots of 5 ml of this solution were pipetted into 19 test-tubes, cooled again to 3 °C and the tubes sealed. The ampoules thus prepared were kept in a thermostat filled with oil at 81.5 ± 0.5 °C for reaction times (*t*) between 0 and 12 h. The reactions were stopped by submerging the ampoules in a cold bath (−78 °C); the ampoules were then stored in a refrigerator (+3 °C).

For the evaluation shown in Figure 1 the decreasing contents of unconsumed acetic acid were titrated potentiometrically, the samples being taken from a reaction flask at the appropriate times.

For Figure 2, the increasing amounts of DCU generated during the course of the reaction were determined gravimetrically. After filtration, the DCU was washed with cold cyclohexane, dried at 105 °C and weighed. The isourea concentrations were calculated from these results.

For Figure 3, the decreasing concentrations of *N*,*N*′-dicyclohexyl-*O*-(1-methylheptyl)isourea were determined on the basis of the C=N—IR absorption at 1665.4 $cm^{-1}$. The test solutions in this case were prepared with spectroscopically pure cyclohexane.

All values were tabulated and then interpreted graphically. The percentage errors were calculated to $\pm$ 1.0%.

## Acknowledgements

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