Study on the Mechanism of Formation of 1-Methylheptyl Phenyl Ether by the Isourea Method

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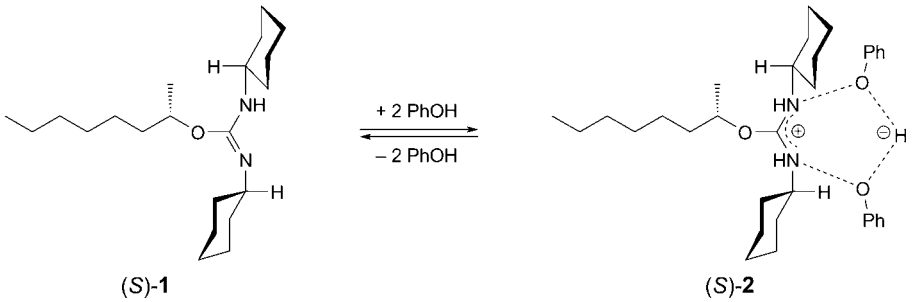
The formation of (1*R*)-1-methylheptyl phenyl ether from (2*S*)-octan-2-ol *via* its isourea derivative (*S*)-**1** follows a borderline mechanism. The intermediacy of a carbocation (see (*S*)-**2**) can be demonstrated (*Scheme 1*). However, the extremely high inversion of configuration and the olefinic by-products are also indicative of an S_N2 mechanism.

Introduction. – Currently increased attention is being dedicated to chiral syntheses, because pure enantiomers are becoming much more important [1]. For example, with the help of the isourea method, it is possible to invert (+)-(2*S*)-octan-2-ol *via* (−)-(1*R*)-1-methylhexyl acetate to the enantiomeric, optically pure (−)-(2*R*)-octan-2-ol [2][3]. The same inversion is also possible with phenol instead of acetic acid as OH-acidic compound. In this way, the enantiomer (−)-(2*R*)-octan-2-ol is isolated from the corresponding phenol ether by means of ozonolysis. However, the rate of inversion of configuration amounts to 99.4%, which is a little lower [2–4]. Thus, both reactions proceed in a highly stereospecific manner.

Results and Discussion. – An analysis of spectrometric results was carried out to obtain a more detailed insight into the structure of the 1:2 adduct (*S*)-**2**, resulting from the (2*S*)-octan-2-ol-derived isourea (*S*)-**1** and phenol (*Scheme 1*), in particular, to gain information about the molecular-structure type [3][5].

Scheme 1



(*S*)-**1** (*S*)-**2**

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First of all, the 1:2 molar ratio of the isourea to phenol in *rac*-**2** was corroborated by the ^{1}H-NMR spectrum (500 MHz; *Table 1*[2])): the two CH groups of the cyclohexane rings of *rac*-**2** were observed as one signal with an intensity of two at δ(H) 3.22 (unresolved *multiplet*). The mobile NH and OH H-atoms appeared as one signal with an intensity of three at δ(H) 7.68 (*s*). Moreover, broadened signals (resolved *m*) at δ(H) 6.85, 6.90, and 7.22 were assigned to the ten H-atoms of the two Ph groups. On the other hand, the aliphatic H-atoms resonated, as expected, in the higher-field region at δ(H) 0.91 and 1.22 (2Me) and 1.13–1.35, 1.48, and 1.60 (unresolved *m*, CH_2) together with the signal of a tertiary H-atom at δ(H) 4.88 (resolved *m*). On the basis of these findings, a chemical formula with homonuclear H-bonds is proposed for (*S*)-**2** (see *Scheme 1*) [6]. As a consequence of this molecular arrangement in (*S*)-**2**, the NH signal at δ(H) 3.38 of the isourea (*S*)-**1** was shifted to lower field at δ(H) 7.68, because in the *rac*-**2** the electronic situations of the two N-atoms are equivalent. Moreover, the two different cyclohexane-CH signals at δ(H) 3.38 and 2.80 of (*S*)-**1** coalesced to one signal at δ(H) 3.22 in *rac*-**2**. Accordingly, a rapid exchange occurred between the mobile NH

Table 1. *^{1}H- and ^{13}C-NMR Data* (500 and 125 MHz, resp.; $CDCl_3$) *of* rac-**2**[a])[2]). δ in ppm, *J* in Hz.

	δ(H)	δ(C)
Me(1)	1.22 (*d*, *J* = 6.1)	19.70
H–C(2)	4.88 (pseudo-*sext.*, *J*(1,2) = *J*(2,3) = 6.1)	73.82
CH_2(3)	1.48, 1.60 (2*m*)	36.29
CH_2(4)	1.13–1.35 (*m*)	25.1
CH_2(5)	1.13–1.35 (*m*)	29.21
CH_2(6)	1.13–1.35 (*m*)	31.75
CH_2(7)	1.13–1.35 (*m*)	37.4
Me(8)	0.91 (*t*, *J* = 7.0)	14.08
C(9)	–	154.01
CH(10,16)	3.22 (*m*)	53.03
CH_2(11)	1.48 (*m*)	33.99
CH_2(12)	1.76 (*m*)	25.26
CH_2(13)	1.61 (*m*)	25.28
CH_2(14)	1.76 (*m*)	25.26
CH_2(15)	1.48 (*m*)	33.99
CH_2(17)	1.48 (*m*)	33.95
CH_2(18)	1.76 (*m*)	25.26
CH_2(19)	1.61 (*m*)	25.28
CH_2(20)	1.76 (*m*)	25.26
CH_2(21)	1.48 (*m*)	33.95
C(22,28)	–	157.52
CH(23,27,29,33)	6.90 (*dd*, J_o = 8.6, J_m = 1.0)	116.07
CH(24,26,30,32)	7.22 (*dd*, J_o = 8.6, 7.4)	129.40
CH(25,31)	6.85 (*dt*, J_o = 7.4, J_m = 1.0)	119.12
OH, 2 NH	7.68 (*s*)	

[a]) See *Fig. 1* for atom numbering.

[2]) Arbitrary atom numbering; for systematic names, see *Exper. Part.*

and OH H-atoms, respectively, of *rac*-**2** which caused them to become equivalent on the NMR time scale: a type of three-point relationship exists between these H-atoms which is responsible for the same chemical shifts of the cyclohexane-CH protons [5]. The broad-band H-decoupled ^{13}C-NMR spectrum was fully consistent with the structure of *rac*-**2** (*Table 1*). Especially, the signals of C(22) and C(28) at δ(C) 157.52 were characteristic for the equivalence of the two phenol molecules. This means that they participate in the cyclic electronic flow involving C(9) and the two N-atoms, respectively, of the initial isourea moiety as shown in *Scheme 1*. A NOESY experiment ($CDCl_3$) with *rac*-**2** revealed the relevant intramolecular ^{1}H, ^{1}H-contacts which were fully consistent with the proposed structure of an isouronium phenolate adduct in solution, with the characteristic feature of a C_2 axis through O–C(9) and the H-atom bridging both phenol O-atoms, an axis which is elongated by the C_8-alkyl chain with free rotation about the O–C(2) bond (*Fig. 1* and *Table 2*). For example, the mobile H-atoms (NH, OH) were spatially vicinal to seven H-atoms (six strong, one weak) within the adduct (aliphatic CH_2 (DEPT) and CH and aromatic CH). Whereas the tertiary H-atom H–C(2) exhibited interactions with eight spatially vicinal H-atoms, the two cyclohexane-CH H-atoms also showed six spatial contacts.

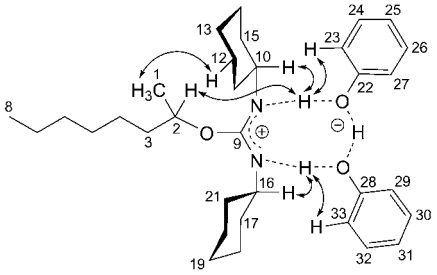


Fig. 1. *Selected NOESY correlations of* rac-**2**[2])

The IR spectrum (film) of adduct *rac*-**2** exhibited a broadened trough in the region 3600 – 2100 cm^{-1}, characteristic for intramolecular H-bonds. The band at 1630 cm^{-1} was indicative of the C=N group. This same band appeared in the solution IR spectrum of *rac*-**2** (0.034M in CCl_4) at 1628 cm^{-1}. In addition, the latter spectrum exhibited a valence oscillation of the C=N group at 1655 cm^{-1} [5]. In an IR spectrum recorded at 100°, the characteristic band for *N*,*N*′-dicyclohexylurea (DCU) at 3320 cm^{-1} was already apparent, as well as a >CH rocking oscillation at 640 cm^{-1}. Accordingly, at this temperature, the crystalline structure of *rac*-**2** was deliquescing since the reaction to form the final products started [5].

X-Ray Crystal-Structure Analysis of (*S*)-2. – On consideration of the above-described spectrometric findings, it must be assumed that the protonated isourea and the phenolate anion exist as a tight ion pair in *rac*-**2**, albeit according to mass determinations only to an extent of 62 – 76% in CCl_4 solution [5][7 – 9].

By means of the X-ray crystal-structure analysis, the trimolecular structure of (*S*)-**2** at 200 K was determined (*Fig. 2*), revealing the ionic character and demonstrating the

Table 2. *Characteristic NOE Data of the Isouronium Phenolate* rac-**2**[a])[2])

Irradiation δ [ppm]	H-atom	Enhancement[b]) δ [ppm]	H-atom
1.22	Me(1)	1.61 (*s*)	H_{eq}–C(13), H_{eq}–C(19)
		1.76 (v*s*)	H_{eq}–C(12), H_{eq}–C(14), H_{eq}–C(18), H_{eq}–C(20)
		4.88 (*s*)	H–C(2)
		6.90 (*m*)	H_o
		7.22 (*w*)	H_m
		7.68 (*m*)	NH
3.22	H–C(10), H–C(16)	7.68 (v*s*)	NH
		4.88 (*w*)	H–C(2)
		1.84 (*s*)	H_{eq}–C(11), H_{eq}–C(15), H_{eq}–C(17), H_{eq}–C(21)
4.88	H–C(2)	1.48 (*w*)	H_b–C(3)
		1.60 (*w*)	H_a–C(3)
		1.84 (*w*)	H_{eq}–C(11), H_{eq}–C(15), H_{eq}–C(17), H_{eq}–C(21)
		3.22 (*w*)	H–C(10), H–C(16)
		6.90 (*w*)	H_o
		7.68 (*w*)	NH
6.85	H_p	7.22 (*s*)	H_m
6.90	H_o	7.68 (*s*)	NH
		7.22 (*s*)	H_m
		1.84 (*w*)	H_{eq}–C(11), H_{eq}–C(15), H_{eq}–C(17), H_{eq}–C(21)
		1.76 (*w*)	H_{eq}–C(12), H_{eq}–C(14), H_{eq}–C(18), H_{eq}–C(20)
7.22	H_m	6.85 (*s*)	H_p
		6.90 (*s*)	H_o
7.68	NH	1.60 (*w*)	H_a–C(3)
		3.22 (*s*)	H–C(10), H–C(16)
		4.88 (*s*)	H–C(2)
		6.90 (*s*)	H_o

[a]) At 500 MHz in $CDCl_3$. [b]) Intensity of signals: very strong (v*s*), strong (*s*), middle (*m*), and weak (*w*).

H-bonds, respectively. This crystalline adduct exists as a dimer as shown in *Fig. 3.* As a consquence of the very rapid exchange of the bonding states, the atomic binding distances of the H-bonds become numerically visible (*Table 3*, *Fig. 3*, *Scheme 2*).

Mechanism. – Analogously to the S_N1/S_N2 mechanism operating during the formation of enantiomerically pure (1*R*)-1-methylheptyl acetate from (2*S*)-octan-2-ol by using the isourea method, olefinic by-products (octenes) are formed in significant yields during the reaction furnishing (1*R*)-1-methylheptyl phenyl ether from the isourea derivative (*S*)-**2**. They are produced following *E*1 and *E*2 mechanisms, respectively, caused by hydride shifts [3][10]. The intermediacy of the carbocation of (*S*)-**2** additionally leads to products of nuclear alkylation, *i.e.*, 2-(1-methylheptyl)phenol and 4-(1-methylheptyl)phenol. These compounds are a confirmation for the intermediacy of a [(1-methylheptyl)oxy]carbenium ion [3].

As the adduct *rac*-**2** exists in the crystalline state as a dimer, the question arises as to the way in which the reaction proceeds. It can be reasoned that at 100° in the molten

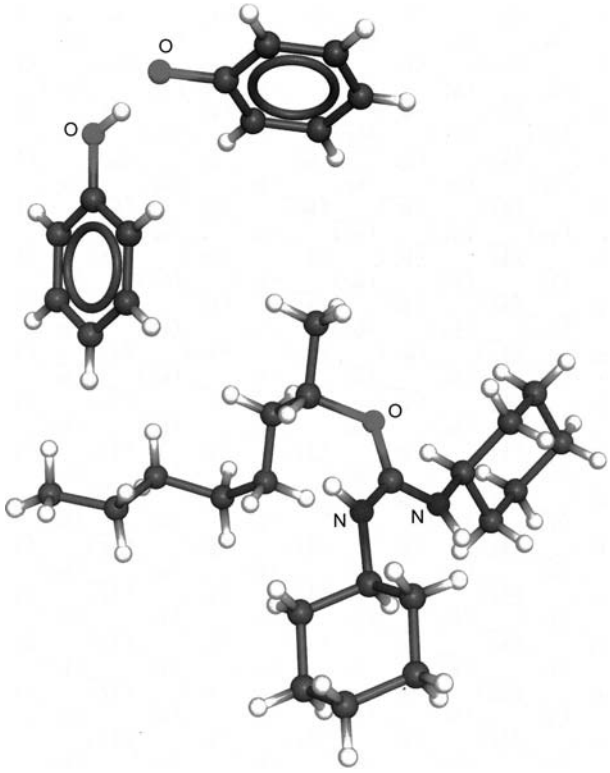


Fig. 2. *X-Ray crystal structure of the trimolecular complex (+)-(*S*)-*N,N′*-dicyclohexyl-*O*-(1-methylheptyl)isouronium phenolate phenol* ((*S*)-**2**)

Table 3. *Bond Lengths of H-Bonds* (*a*) *and Covalent Bonds* (*b*) *in the Crystal of (*S*)-***2*** (see Fig. 3, Scheme 2*)

H-Bond	Length [Å]
(N)1···H···O	0.96 (*b*)
N(1)···H···O	1.83 (*a*)
N(2)···H···O	0.94 (*b*)
N(2)···H···O	1.84 (*a*)
O···H···O	0.95 (*b*)
O···H···O	1.51 (*a*)

state in the absence of any solvent and without an excess of phenol, analogously to an acetolysis, a phenolysis occurs. Thus, analogously to the formation of (1*R*)-1-methylheptyl acetate, a tight ion pair results, which reacts subsequently *via* a borderline mechanism to afford the (1*R*)-1-methylheptyl phenyl ether (ROPh) and *N,N′*-dicyclohexylurea (*Eqn. 1*) [8][11].

$$(\mathrm{ROiU})^{+}(\mathrm{PhO})^{-} \rightleftharpoons \mathrm{ROPh} + \mathrm{DCU} \qquad (1)$$

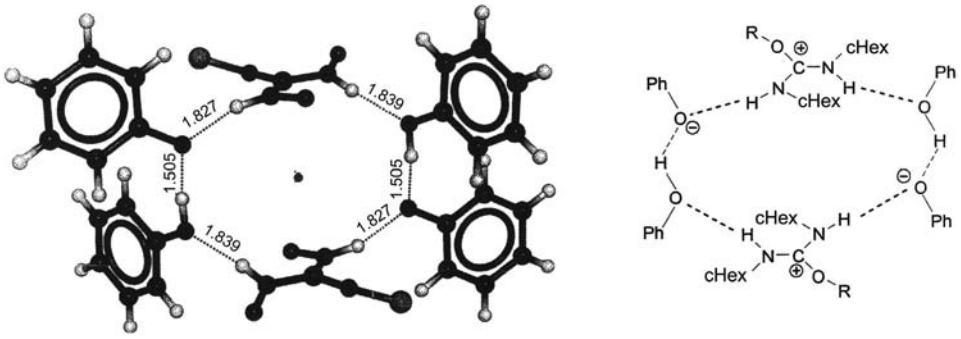
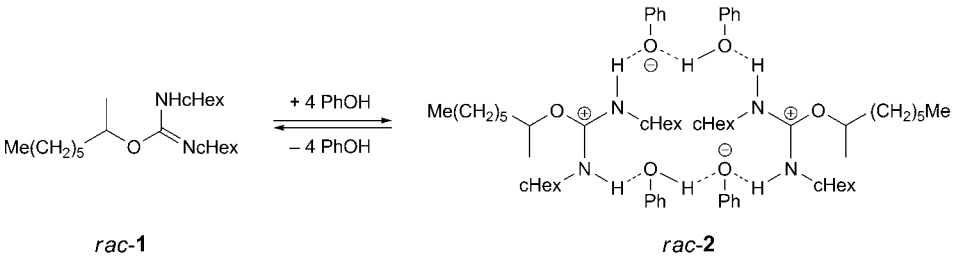


Fig. 3. *View of* (S)-N,N′-*dicyclohexyl*-O-*(1-methylheptyl)isouronium phenolate phenol* (*(*S*)-***2***) as dimer in the crystalline state showing H-bonds.* R = alkyl chain, cHex = cyclohexane, Ph = phenol, ● = C_2 symmetry center.

Scheme 2



rac-**1** *rac*-**2**

The intermediate [(1-methylheptyl)oxy]carbenium ion is strongly shielded in this pathway by the two bulky cyclohexylamino residues so that a nucleophilic attack from the back is totally hindered. In spite of the detected partial S_N1 process, racemization is nearly impossible: an inversion of configuration of 99.4% occurs [3][8]. According to [12], a cation such as the one present in *rac*-**2** may have sufficient stability and a sufficiently long lifetime due to hyperconjugation to ensure participation in the S_N1 mechanism, too (*cf.* [1][8]).

Conclusions. – From the above considerations, the formation of (1*R*)-1-methylheptyl phenyl ether from (2*S*)-octan-2-ol *via* (*S*)-**2** followed a borderline mechanism. The reaction proceeded with almost complete inversion of configuration (99.4%).

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Experimental Part

General. The racemic compound *rac*-**1** was resolved by the method of *Vogel* [13]. The synthesis of (−)-(1*R*)-1-methylheptyl phenyl ether (ROPh), the ozonolysis of this ether (→ (2*R*)-octan-2-ol), and the isolation of the *C*-(1-methylheptyl)-substituted phenols are reported elsewhere [3]. IR Spectra: *Perkin-*

Elmer-421 spectrophotometer; $\tilde{\nu}$ in cm^{-1}. NMR Spectra: *Bruker-DRX-500-Avance* spectrometer (*Bruker Biospin GmbH*); at 500.13 (^1H) and 125.76 MHz (^{13}C); δ in ppm rel. to residual $CHCl_3$ in $CDCl_3$, *J* in Hz.

(1S)-1-Methylheptyl N,N′*-Dicyclohexylcarbamimidate* ((*S*)-**1**). ^1H-NMR: 4.91 (pseudo-*sext.*, H–C(2)); 3.38 (*m*, NH, H–C(10)); 2.80 (*m*, H–C(16)); 1.93 (*m*, CH_2(11,15)); 1.73 (*m*, CH_2(12,14,17,18,20,21)); 1.60 (*m*, 1 H of CH_2(3), CH_2(13,19)); 1.46 (*m*, 1 H of CH_2(3)); 1.32–1.00 (2*m*, 18 H); 1.20 (*d*, Me(1)); 0.90 (*t*, Me(8)); $J(1,2) = J(2,3) = 6.2$. ^{13}C-NMR: 150.61 (C(9)); 69.86 (C(2)); 54.68 (C(10)); 50.17 (C(16)); 34.93 (C(3)); 34.58* (C(11,15)); 34.54* (C(17,21)); 31.81 (C(6)); 29.35 (C(5)); 26.09** (C(13)); 25.78 (C(19)); 25.22; 25.17; 25.09; 25.05 (C(12,14,18,20,4)); 22.59 (C(7)); 19.64 (C(1)); 14.08 (C(8)).

Bis(cyclohexylamino)[(1-methylheptyl)oxy]methylium Phenoxide Phenol (1:1:1) (*rac*-**2**). ^1H- and ^{13}C-NMR: *Table 1*.

The X-ray crystal-structure analysis of *rac*-**2** was performed with an *Oxford-Diffraction-Xcalibert* single-crystal X-ray diffractometer (*Oxford Diffraction Ltd.*) and a sapphire CCD detector. For the crystallographic data, see *Table 4* (structure solution with SHELXS97 [14]). CCDC-943846 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge *via* http://www.ccdc.cam.ac.uk/data_request/cif.

Table 4. *Crystallographic Data of* rac-**2**

Formula	$C_{21}H_{41}N_2O \cdot 2\ C_6H_5O$	V [Å^3]	1555.6(4)
M_r	524.77	Z	2
Crystal color	colorless	Reflections coll., unique	8621, 4426
Crystal dimensions [mm]	$0.08 \times 0.06 \times 0.04$	2θ Range [°]	2.56–27.89
Temperature [K]	200	Structure factor, $F(000)$	576
Wavelength MoK_α [Å]	λ 0.71073	D_x [g cm^{-3}]	1.120
Crystal dimensions [mm]	$0.08 \times 0.06 \times 0.04$	Reflections used	1950
Crystal system	triclinic	Parameters refined	371
Space group	*P*1	Final R ($I > 2\sigma(I)$ reflections)	$R_1 = 0.0729$, $wR_2 = 0.1362$
Unit-cell dimensions:			
a [Å]	11.577	R indices (all data)	$R_1 = 0.1569$, $wR_2 = 0.1811$
b [Å]	12.516	Goodness of fit, F^2	1.507
c [Å]	13.111	Extinction coefficient	0.0057(13)
α [°]	66.54	Diffraction radiation	graphite
β [°]	81.11	monochromator	
γ [°]	63.26		

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