Pergamon

Tetrahedron Vol. 50, No. 42, pp. 12211-12218, 1994

0040-4020/94 $7.00+0.00

0040-4020(94)00767-5

Stereoisomerism in N-Cyano-O-phenylisoureas and Related Compounds

Peter J Garratt and Simon N Thorn

Department of Chemistry, University College London, 20 Gordon Street, London WC1H 0AJ

Roger Wrigglesworth

Sandoz Institute for Medical Research, Gower Place, London WC1E 6BN

Abstract: *The barriers to interconversion of the stereomers of a number of N-cyano-O-phenylisoureas and related systems have been examined by variable temperature ^1H NMR spectroscopy. Rate constants were determined from the coalescence temperature using the Gutowsky-Holm equation, and free energies of activation then derived using the Eyring equation. The effect of structure on the rate process is discussed in relation to the bond-rotation and nitrogen-inversion mechanisms and it is concluded that the observations are best explained by a mixture of mechanisms.*

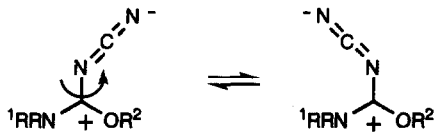
Introduction

N-Cyano-O-phenylisoureas (**1**) exist as mixtures of two isomers at ambient temperature, as shown by the ^1H NMR and ^{13}C NMR spectra. Gradually heating the samples causes the signals in these spectra to broaden, coalesce and then, at higher temperatures, again exhibit well resolved spectra. The process is reversible, the isomeric mixture again being obtained on cooling the sample to ambient temperature. Such behaviour is shown by many other systems containing the C=N bond and represents the equilibration between the syn-anti structures (**1a**-**1b**) taking place slowly on the NMR timescale at ambient temperatures.[1]

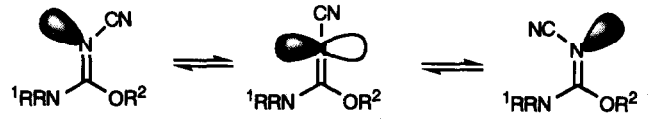
1a **1b**

Two extreme mechanisms have been suggested for this interconversion about the C=N bond.

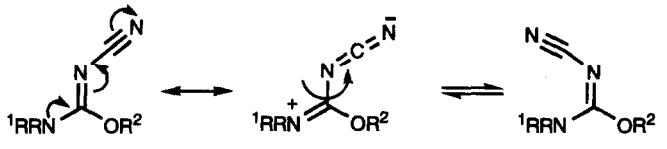
1) Charge transfer reduces the double bond character of the C=N bond and rotation about the bond occurs. During this process the sp^2 hybridization of the nitrogen is retained and the bond angle does not change in the process.



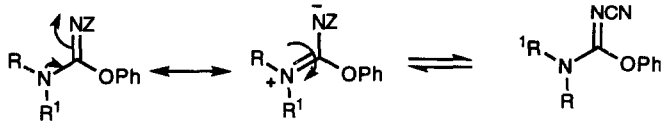
2) Inversion of the imine nitrogen through a linear C-N-CN transition state in the plane of the isourea. In this, the lateral shift mechanism, the C-N-CN bond angle increases to 180° in the transition state and the C=N bond is, to the first approximation, unaffected.



In the case of rotation, the electron-donating power of the attached heteroatoms could have an effect, leading to a lowering of the C=N rotational barrier but an increase in the C-N, C-O single bond rotational barriers.



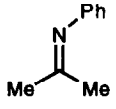
This later process, with the implied partial double bond character of the RR^1N-C bond, also presents the possibility of restricted rotation about this bond and the introduction of another temperature dependent process.[2]



The two mechanisms might be expected to be distinguishable by an examination of the effects of substituents and solvents on the rate of isomerisation. Groups that reduce the double bond character of the imine C=N bond would be expected to lower the interconversion barrier if

the process proceeds by rotation, whereas they should have little effect if the process proceeds by nitrogen inversion. Electron withdrawing substituents on the imine nitrogen should increase the s character of the unshared electron pair, which must be rehybridized into a p-orbital in the transition state for the inversion mechanism thus raising the barrier to interconversion. Steric effects, by contrast, might raise the ground state energy without increasing the transition state energy for inversion and thus lead to a lowering of the barrier in this case. In the rotational mechanism, charge separation occurs and thus increasing the polarity of the solvent should increase the rate of interconversion, whereas the solvent polarity should have little effect on the inversion mechanism.

There has been considerable discussion as to which of these mechanisms operate in imines of this type. The inversion mechanism was favoured for the N-phenylamine **2** which shows an unexpectedly low barrier to interconversion of 21 kcal mol^{-1}.[3] In the transition state for inversion, the phenyl ring could conjugate with the developing p-orbital. Similar effects on lowering the interconversion barrier are observed with other groups that can stabilise the transition state by conjugative overlap.[2,4] The two mechanisms are, of course, not mutually exclusive and Carlson et al. [5] suggested that a mixed mechanism may apply to interconversions of this type. In the two extremes, the C-N-CN bond angle in the transition state is 120° for the rotational mechanism, and 180° for the inversion mechanism. Clearly, a bond angle between these extremes would allow a contribution from both mechanisms, and those substituents favouring bond rotation should lead to a smaller bond angle, while those favouring inversion should lead to an increased bond angle.



2

In the course of synthetic studies aimed at the preparation of hexahydro-pyrimidines,[6-9] compounds of considerable biological importance and pharmaceutical value, we have prepared a considerable number of N-cyano-O-phenylisoureas and related compounds, and we have examined their dynamic behaviour by temperature variable ^1H NMR spectroscopy. The results of these studies are now described.

Results and Discussion

The N-cyano-O-phenylisoureas and related compounds were prepared by previously described methods. The results of the variable temperature ^1H NMR spectroscopy experiments are tabulated in Tables 1-3. The rate constant, k', of the chemical exchange at the coalescence temperature T_c was calculated from equation 1.[10] Equation 1 is strictly valid for two states having equal populations and lifetimes, but the errors introduced by deviations from these conditions are small. The line separation, $\Delta\upsilon$, is taken at a temperature where exchange is slow, and the signal width must be small in comparison to it. The rate constant is related to the free energy of

activation by the Eyring equation (equation 2).[11] Assuming the transmission coefficient, **k**, to be unity, the free energy of activation, $\Delta G^{\ddagger}$, can be calculated from equation 3.

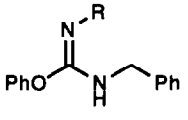
$$k' = \pi\Delta\upsilon/\sqrt{2} \qquad \text{equation 1}$$

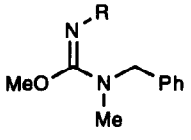
$$k' = \mathbf{k}(K_B T/h)\, e^{-\Delta G/RT} \qquad \text{equation 2}$$

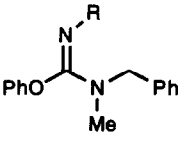
$$\Delta G^{\ddagger} = RT_c[\ln T_c - \ln k' + 23.760] \qquad \text{equation 3}$$

Table 1

Compound	Solvent	Isomer ratio	T_c, K	$\Delta\upsilon$, Hz	k'^{-1}, s^{-1}	$\Delta G^{\ddagger}$ kcal mol-1	σ_p[12]
1a	$CDCl_3$	10:1	308	34.50	77	15.4	0.66
1a	DMSO	1.2:1	322	38.19	85	16.0	0.66
1b	CD_2Cl_2	1:1	279	5.12	11	14.9	0.36
1c	DMSO		>443			>25	0.80
1d	CD_2Cl_2	1:1	299	5.92	13	16.0	0.31
1e	$CDCl_3$	1:1	286	5.96	13	15.3	(< 0.80)
3	$CDCl_3$	2:1	263	140.66	312.5	12.3	0.66
4a	$CDCl_3$	1:1	283	19.31	43	14.4	0.66
4b	$CDCl_3$	1.5:1	328	50.42	112	16.0	0.80







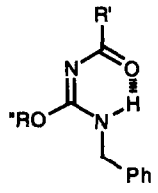
1a R = CN
1b R = $CONH_2$
1c R = $COCF_3$
1d R = $COCH_3$
1e R = $OCOCF_3$

3 R = CN

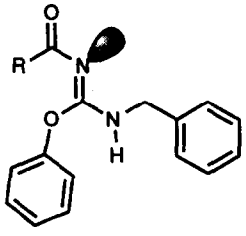
4a R = CN
4b R = $COCF_3$

Table 1 gives the results for a group of isoureas of similar structure, differing mainly in the nature of the substituent, R, on the imine nitrogen. The variation in the free energy of activation is not large, except for compound **1c**, where only one isomer can be observed up to 170 °C. The isomer ratios are reasonably close to unity except for compound **1a** in $CDCl_3$. The electron withdrawing effect (EWE) of R can be correlated with the Hammett σ_p values. The compounds in order of decreasing EWE for R are **1c** > **1a** > **1b** > **1d**, and a decreasing free energy of activation is found except for **1d**, which appears too high. This would suggest that in this case inversion is the principal mechanism, since the EWE would be expected to facilitate the bond rotation process. Other factors may, however, occur. Thus the carbonyl compounds might be expected to hydrogen bond to the amine hydrogen, as illustrated in **5**. This would be expected

to stabilise this structure and the isomer ratio should deviate from one. This is observed for **1c**, which occurs as one isomer but is not the case for compounds **1b** and **1d**, where the isomer ratio is unity, which suggests that there are other factors involved. The lower value for $\Delta G^{\ddagger}$ for the N-methyl substituted analogue **4b** of **1c** does support a role for hydrogen bonding. It is possible that the non-hydrogen-bonded structure represented by **6** is less sterically crowded than the hydrogen-bonded structures and that the energetically preferred structure then depends on the strength of the hydrogen bond in a particular derivative. This would suggest that the preferred structure for **1a** is that with the CN on the same side as the O-phenyl group, and this preference is greater in $CDCl_3$ than in DMSO. The equivalence of the two isomers of **4a** indicates that replacing the N-H of **1a** with N-Me causes the phenyl group on oxygen to adopt a s-cis orientation to the C=N group, thus making both orientations of the C≡N group energetically the same.



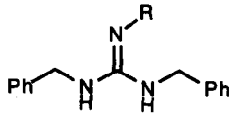
5

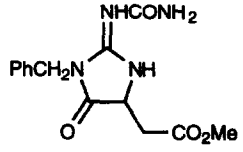


6

Table 2

Compound	Solvent	Isomer ratio	T_c, K	$\Delta\upsilon$, Hz	k'^{-1}, s^{-1}	$\Delta G^{\ddagger}$ kcal mol-1	σ_p, R
7a	CD_2Cl_2		<193			<5	0.66
7b	$CDCl_3$	1:1	278	65.42	145	13.5	0.36
7c	$CDCl_3$	1:1	301	86.75	193	14.5	0.80
7d	$CDCl_3$	1:1	273	80.86	180	13.1	0.50
8	CD_2Cl_2		<193			<5	0.36





7a R = CN
7b R = $CONH_2$
7c R = $COCF_3$
7d R = $COCH_3$

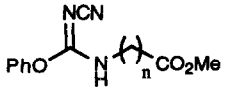
8

Table 2 gives the results for a corresponding group of guanidines. In compounds **7a - d**, the equilibrating structures are identical so the ratio of isomers is necessarily 1:1. The lower barrier to rotation of **7a** compared to the carbonyl derivatives suggests that the latter are

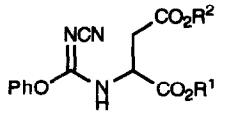
stabilised by hydrogen bonding, resulting in a larger activation energy for interconversion. Again, the derivative with the CF_3CO group, **7c**, has the highest barrier, as expected for the strongest hydrogen bond. In this case, however, the difference is not large and this probably reflects the fact that both interconverting isomers are hydrogen bond stabilised whereas only one isomer is stabilised in the case of compound **1c**. In **8**, the low barrier probably reflects competition by the ester group for hydrogen bond formation.

Table 3

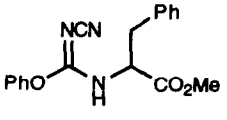
Compound	Solvent	Isomer ratio	T_c, K	$\Delta\upsilon$, Hz	k'^{-1}, s^{-1}	$\Delta G^{\ddagger}$ kcal mol-1
9a	DMSO	1.3:1	343	60.00	133	16.8
9b	DMSO	1.2:1	323	57.00	127	15.9
10a	DMSO	1.3:1	333	66.50	148	16.3
10b	$CDCl_3$	1.2:1	318	44.10	98	16.0
10c	$CDCl_3$	1:1	315	31.70	70	15.8
11	$CDCl_3$	3:1	315	25.89	57.5	15.9
12a	$CDCl_3$	2.8:1	301	20.40	45	15.3
12b	$CDCl_3$	2.7:1	302	19.60	43.5	15.5
13a	$CDCl_3$	1.2:1	313	83.89	186	15.1
13b	$CDCl_3$	1:1	348	96.13	214	16.8
14a	$CDCl_3$	1.05:1	289	22.18	49	14.7
14b	$CDCl_3$		<213			<5
15	$CDCl_3$	2:1	333	91.53	203	16.1
16	$CDCl_3$	1.75:1	333	94.25	209	16.0



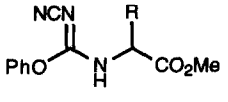
9a n = 1
9b n = 2



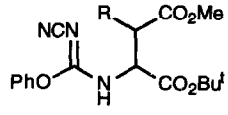
10a $R^1 = R^2 = Me$
10b $R^1 = {}^tBu$, $R^2 = Me$
10c $R^1 = Me$, $R^2 = {}^tBu$



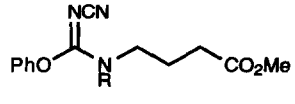
11



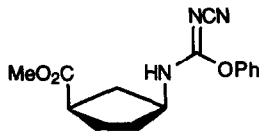
12a R = CH_3
12b R = CH_2CH_3



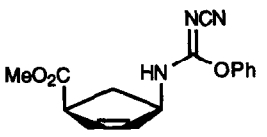
13a R = $CH_2CH_2CH_3$
13b R = CH_2Ph



14a R = CH_3
14b R = $OCOCH_2Ph$



15



16

The compounds in Table 3 all have the cyano group as the N-substituent and hydrogen bonding should not influence the C≡N portion of the molecule. The compounds all show quite similar energies of activation and the variations in isomer ratio are also quite small, that for compound **11** being the largest at 3:1. The isomer preferences are likely to be based on steric differences between the two forms. Compounds with a secondary carbon atom attached to the amine nitrogen generally have greater isomer ratios, but the effect is usually small (compare **9** with **10**). That the isomer ratios for **12a, b** are less than that for **11** may indicate that **12a, b** adopt a conformation in which the group substituting nitrogen is permanently away from the NCN function. The preference for one isomer shown by the cyclopentyl **15** and cyclopentenyl **16** derivatives may arise from both steric preference and hydrogen bonding between the 1,4-substituents.

Increasing the electronegativity of the substituent attached to the imine nitrogen generally leads to an increase in the activation barrier (see Table 1), as expected for the nitrogen inversion model, since the s character of the nitrogen lone pair is increased. Many other factors, such as hydrogen bonding and steric interactions, contribute to the ground state and transition state energies of these systems, and the complex variation of $\Delta G^{\#}$ with structural change suggests that there is a mixture of mechanisms.[5]

Experimental

IR spectra were taken on a Perkin-Elmer PE-983 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian VXR-400 (400 MHz) spectrometer and are reported in δ values relative to tetramethylsilane as internal standard. ^{13}C NMR spectra were recorded at 50 MHz. Mass spectra were obtained on a VG ZAB-2F spectrometer at the School of Pharmacy, University of London. Column chromatography was carried out with Merck flash silica (200-400 mesh) as stationary phase.

Preparation of N-cyano-N'-(4-methoxycarbonylcyclopent-2-enyl)-O-phenylisourea (16)
Triethylamine (0.65 g, 6.5 mmol) was added to a stirred suspension of cyclopentenylamine hydrochloride (1.10 g, 6.4 mmol)[13,14] in propan-2-ol (50 mL). Diphenyl cyanocarbonimidate (1.54 g, 6.5 mmol) was added and the resulting solution stirred at RT for 8 h. The solvent was removed by evaporation under reduced pressure and the residue purified by flash chromatography, eluting with ethyl acetate: cyclohexane (1:1) to give **16** as a white solid, 1.62 g (5.7 mmol, 89%). MS, *m/e*, 285.1127 ($C_{15}H_{15}N_3O_3$ requires 285.1113), 285, 226, 125, 94; ^{1}H NMR, $CDCl_3$, δ, 7.45 -7.39 (m, 2H), 7.36-7.30 (m, 1H), 7.29 - 7.10 (m, 2H), 6.62 (bd), 6.08 - 5.90 (m), 5.08 - 4.96 (m), 3.79 (bs), 3,57 (bs), 3.61 - 3.46 (m), 2.60-2.52 (m), 2.42 -2.33 (m), 2.26 -2.16 (m), 1.91 -1.88 (m); ^{13}C NMR, $CDCl_3$, δ, 173.7, 162.6, 150.9, 134.1, 133.5, 132.9, 132.5, 130.4, 129.6, 127.35, 126.7, 121.4, 115.0, 57.9, 52.8, 52.4, 49.6, 49.2, 34.2, 33.9; IR, $CHCl_3$, 3052, 2191, 1732, 1718, 1615 cm^{-1}.

Preparation of N-cyano-N'-(3-methoxycarbonylcyclopentyl)-O-phenyl-isourea (15).
To a stirred solution of **15** (0.25 g, 0.87 mmol) in degassed ethanol (10mL) was added Pd /charcoal (10%, 0.01g) and the resulting suspension was stirred under an atmosphere of hydrogen (1 atm) for 8 h. The reaction mixture was diluted with ethanol (20 mL), filtered through celite and the solvent removed by evaporation under reduced pressure to give **15** as a white solid 0.24 g (8.3 mmol, 96%). MS, *m/e*, 288.1361 (MH^+, $C_{15}H_{18}N_3O_3$ requires 288.1348), 288 (MH^+), 256, 127,67; ^{1}H NMR, $CDCl_3$, δ, 7.47 - 7.38 (m, 2H), 7.36 - 7.25 (m, 1H), 7.14 - 7.08 (m, 2H), 4,44 - 4.32 (m), 3.76 (s), 3.54 (s), 3.01-2.85 (m), 2.32 - 1.65 (m); ^{13}C NMR, $CDCl_3$, δ, 176.8, 163.1, 151.0, 130.4, 129.6, 127.2,

126.65, 121.4, 121.35, 115.15, 114.9, 55.0, 54.5, 52.5, 41.85, 41.5, 35.9, 35.3, 33.4, 33.3, 28.65, 28.15; IR, $CHCl_3$, 3286, 2191, 1722, 1615 cm^{-1}.

Variable temperature ^1H NMR spectra were obtained on a Varian VXR-400 spectrometer and temperatures were measured at the probe (± 0.1 °C). Samples were allowed to equilibrate for 10 min at each temperature before recording the spectrum.

Acknowledgments: SNT thanks the Science & Engineering Research Council (U.K.) for a studentship. We thank the University of London Intercollegiate Mass Spectrometry Service (School of Pharmacy) for the mass spectra.

References

(1) Oki, M. *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*; VCH: Florida, 1985; Vol. 4.

(2) Kessler, H.; Liebfriz, D.; Burk, C. *Tetrahedron* ,**1970**, *26*, 1805.

(3) Curtin, D. Y.; Grubbs, E. J.; McCarty, C. G. *J Am Chem Soc* ,**1966**, *88*, 2775.

(4) Anet, F. A. L.; Trepka, R. D.; Cram, D. J. *J Am Chem Soc* ,**1967**, *89*, 357.

(5) Carlson, E.; Jones, F. B.; Raban, M. *J Chem Soc, Chem Commun* ,**1969**, 1235.

(6) Garratt, P. J.; Hobbs, C. J.; Wrigglesworth, R. *J Org Chem* ,**1989**, *54*, 1062.

(7) Besse, R.; Garratt, P. J.; Hobbs, C. J.; Rogers, H. M.; Sueliman, A. M.;Walpole, C.S.J ;Wrigglesworth, R. *Tetrahedron* ,**1990**, *46*, 7803.

(8) Garratt, P. J.; Thorn, S. N.; Wrigglesworth, R. *Tetrahedron Letters* ,**1991**, *32*, 691.

(9) Garratt, P. J.; Thorn, S. N.; Wrigglesworth, R. *Tetrahedron* ,**1993**, *49*, 165.

(10) Gutowsky, H. S.; Holm, C. H. *J Chem Phys* ,**1956**, *25*, 1228.

(11) Glasstone, S.; Laidler, K. J.; Eyring, H. *The Theory of Rate Processes*; McGraw-Hill: New York, 1941, Ch1.

(12) Hansch, C; Leo, A. *Substituent Constants for Correlation Analysis in Chemistry and Biology*; John Wiley: New York, 1979.

(13) Kam, B. L.; Oppenheimer, N. J. *J Org Chem* , **1981**, *46*, 3268.

(14) Jagt, J. C.; van Leusen, A. M. *J Org Chem* , **1974**, *39*, 564.

(*Received in UK* 24 *June* 1994; *revised* 30 *August* 1994; *accepted* 2 *September* 1994)