E/*Z* Conformational equilibrium of N-substituted 2*H*-yran-2-imines

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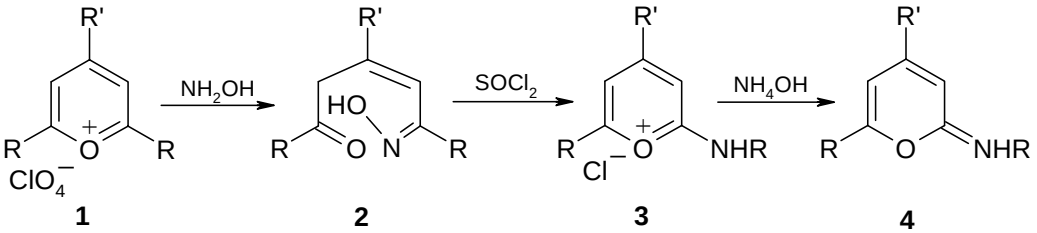
Abstract

Prevailing *Z*-conformations were found in *N*-aryl(or alkyl)substituted 2*H*-pyran-2-imines **4a-e** on the NMR time scale. Conformational assignment was based on ^{1}H and ^{13}C NMR chemical shifts as well as on induced shifts by LSR. The barrier of *E*/*Z* interconversion ($\Delta G^{\neq}_{Tc}$) was calculated from variable temperature ^{1}H-NMR spectra.

Keywords: Heterocycles, *E*,*Z* conformation at C,N double bond, ^{1}H-DNMR

Introduction

We have previously reported the ring-transformation reaction of pyrylium salts **1** into 2-aryl(or alkyl)amino-4,6-disubstituted pyrylium chlorides **3**. Reacting with hydroxylamine, pyrylium salts **1** with bulky α-substituents (such as Ph, *t*Bu, *i*Pr) provided isolable open-chain derivatives **2**, with "*cis*" C,C double bond and "*anti*" oxime, as depicted (Scheme 1). The Beckmann reaction of **2** with thionyl chloride occurred with subsequent cyclization leading to pyrylium cation possessing an aryl(or alkyl) amino substituent in 2-position of the ring.[1]

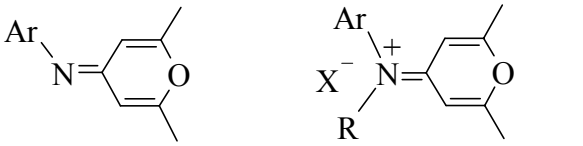


R = Ph, *t*Bu, *i*Pr; R' = Me, Ph

Scheme 1

Treatment of salts **3** with aqueous ammonia gave the pyran 2-imines **4**. Compounds **4** were found to exhibit at the NMR time scale *E*, *Z*-conformational equilibrium at the exocyclic C, N

bond. Surprisingly, no experimental evidence for such equilibrium was provided by earlier reports on *N*-4,6-triphenylpyran 2-imine (**4**, R = R' = Ph)[2-5] or other pyran 2-imines[6,7] and benzoannelated analogs[8-13]. By contrast, the hindered rotation around C,N double bond in N-aryl-2,6-dimethyl-4*H*-pyran-4-imines **5** and related iminium salts **6**, **7** (Scheme 2) had been extensively investigated by ^{1}H, ^{13}C and ^{15}N NMR in the early eighties.[14-18]

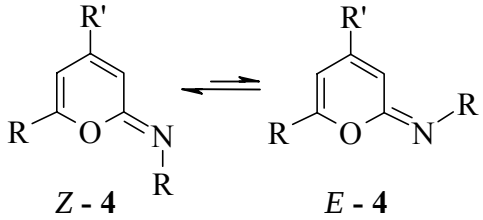


5 **6** (R = H); **7** (R = Me)

Scheme 2

Results

In the series of pyran 2-imines **4a-e**, the ^{1}H and ^{13}C NMR spectra recorded at room temperature displayed two sets of signals (except for **4c**), assigned to *E*, *Z*-conformers at the exocyclic C,N bond. With *E*/*Z* ratio far from 50:50 for all five compounds investigated, the two sets of chemical shifts are readily separated. For each conformer, the individual ^{1}H and ^{13}C resonances were unambiguously assigned using 2D experiments (COSY, HETCOR and COLOC) and are displayed in Tables 1 and 2.



Z - **4** *E* - **4**

4	R	R'
a	Ph	Ph
b	Ph	Me
c	*t*Bu	Me
d	*i*Pr	Me
e	*i*Pr	Ph

Scheme 3

Table 1. ^{1}H-NMR Data: δ_H [ppm], *coupling constants* [Hz] and molar fraction of *E*, *Z*-**4** (solv. $CDCl_3$, 20°C)

	R-N	H-3	R'-4	H-5	R-6
4a *Z* (0.75)	7.27[a] ; 7.10 - 7.34	6.65	7.43 - 7.60 [b]	6.69	7.60[a] ; 7.34 - 7.37
E (0.25)	7.02[a] ; [b]	6.38		6.65	7.90[a] ; [b]
4b *Z*(0.65)	7.24[a] ; 7.12 - 7.37	6.26	2.13	6.29	7.57[a] ; 7.37
E (0.35)	6.99[a] ; [b]	5.99	2.01	6.27	7.88[a] ; [b]
4c *Z* (1.00)	1.34	5.86	1.91	5.43	1.24
4d *Z*(0.92)	1.14 ; 3.94 *7*	5.86	1.91	5.37	1.18 ; 2.57 *7*
E (0.08)	1.15 ; 3.57 *7*	5.86	1.98	5.37	1.18 ; 2.57 *7*

4e *Z* (0.96)	1.20 ; 4.00 *7*	6.34	7.38 - 7.50[b]	5.86	1.25 ; 2.67 *7*	
E (0.04)	1.20 ; 3.70 *7*	6.28		5.82	1.25 ; 2.67 *7*	

[a] aromatic protons in *ortho*-position; [b] obscured by signals of the prevailing conformer.

Table 2. ^{13}C-NMR Data: δ_C [ppm] of *E*, *Z* - **4** (solv. $CDCl_3$, 20ºC)

	C-2	R-N	C-3	C-4	R'-4	C-5	C-6	R-6
4a *Z*	151.9	146.6[a]; 122.6[b]	114.7	146.4	136.5[a]; 126.0[b]	100.2	156.8	131.8[a]; 124.8[b] 128.7[c]; 130.1[d]
E	157.9	128.6[c]; 123.4[d] 147.7[a]; 121.8[b] 129.3[c]; 123.1[d]	105.8	148.0	129.0[c]; 129.6[d] 136.6[a]; 126.2[b] 128.6[c]; 129.8[d]	100.0	158.2	131.7[a]; 125.5[b] 128.9[c]; 130.4[d]
4b *Z*	152.0	147.9[a]; 122.7[b]	116.1	146.1	21.4	103.3	156.0	131.8[a]; 124.8[b] 128.7[c]; 130.1[d]
E	158.0	128.7[c]; 123.3[d] 146.7[a]; 122.0[b] 129.4[c]; 123.0[d]	107.9	148.0	21.5	102.3	157.4	131.7[a]; 125.5[b] 128.8[c]; 130.3[d]
4c *Z*	150.9	30.0[e]; 52.6[f]	116.0	142.4	20.9	99.9	167.7	28.2[e]; 35.3[f]
4d *Z*	152.2	23.8[g]; 45.4[h]	114.6	143.1	21.0	101.0	165.0	20.1[g]; 32.3[h]
E	157.2	24.1[g]; 46.8[h]	105.2	146.2	21.5	100.0	167.3	20.2[g]; 32.3[h]
4e *Z*	152.3	23.7[g]; 45.8[h]	113.7	143.9	137.1[a]; 125.9[b]	98.1	166.1	20.1[g]; 32.7[h]
E	157.1	24.1[g]; 47.1[h]	103.6	146.6	128.8[c]; 129.1[d] 137.6[a]; 126.2[b] 128.8[c]; 129.4[d]	97.4	168.3	20.2[g]; 32.7[h]

[a] C_q; [b] 2CH-*ortho*; [c] 2CH-*meta*; [d] CH-*para*; [e] **Me$_3$**C; [f] Me$_3$**C**; [g] **Me$_2$**CH; [h] Me$_2$**CH**

The stereochemical assignment was performed as follows: in each pair of conformers, the upfield signal for the C-3 atom of the pyran ring (Table 2) was assigned to *E*-conformation, according to the general trend for α-carbons in compounds with C,N double bond.[19] The chemical shift difference between C-3 signal in *E*-**4** and in *Z*-**4** is almost constant in the series (8–10 ppm) and agrees with the difference between C-3 and C-5 signals in the pyran 4-imines **5**,[16] accounting for the same effect of the nitrogen substituent R. The H-3 signals (Table 1) supported this assignment: in the N-phenyl substituted imines **4a**, **4b** this signal is shifted upfield in the *E*-conformer by 0.27 ppm, while much smaller differences (up to 0.06 ppm) are observed

in the *E*, *Z* pairs of the N-alkyl substituted imines **4d**, **4e**. In *E*-**4a** (**4b**) the H-3 atom is shielded by the aromatic ring on nitrogen, non-coplanar with the pyran ring because of steric crowding.

An independent conformational proof was provided by the shifts induced with lanthanide shift reagents (LSR). In Fig. 1 are given the molar induced shifts (MIS in ppm, slopes in representation of induced shifts *vs* molar ratio between LSR and substrate) for imine **4b**, with $Eu(fod)_3$ as LSR.

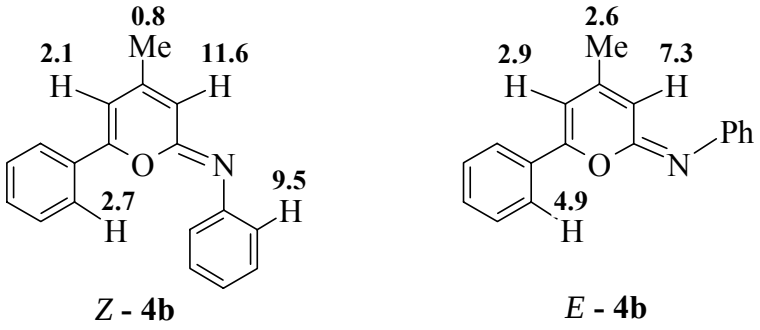


Figure 1. Molar induced shifts (MIS, ppm) in the ^{1}H NMR spectra of *E*, *Z*-**4b** with $Eu(fod)_3$ in $CDCl_3$.

The results for *Z*-**4b** (prevailing conformer) were rationalized by assuming the paramagnetic center of the shift reagent complex to be on the axis of the lone-pair orbital on nitrogen.[20] This renders the substituent on nitrogen and the H-3 atom as closest neighbours to the lanthanide, in agreement with these groups having the highest MIS values. The results for the minor *E*-conformer were less clear-cut, meaning that the geometry of complexation is not obvious (contribution of the oxygen lone-pairs is not precluded). Still, the MIS value for the *ortho*-hydrogens of 6-Ph substituent are higher in *E*-**4b** than in *Z*-**4b**, suggesting reversal of the nitrogen lone-pair. Similar observations were made with *E*, *Z*-**4d** as substrate. In conclusion, the results obtained with LSR are meaningfully correlated with the conformational assignment based on chemical shift values.

The *E*, *Z* equilibrium composition in $CDCl_3$ (see Table 1) is strongly biased towards *Z*-conformer, compound **4c** appearing as single *Z*-conformer.

The free energy of activation at the coalescence temperature ($\Delta G^{\neq}_{Tc}$) for *E*, *Z*-interconversion was determined from variable temperature ^{1}H-NMR spectra (Table 3). The spectral parameters of the signals monitored for coalescence given in the table were measured at 20ºC. Corrections for temperature dependence of δν values have been applied. The precision in coalescence temperature T_c measurement was ± 2K. The rate constants k were evaluated from equations for unequally populated doublets[21a] and the $\Delta G^{\neq}$ values were calculated from Eyring equation, assuming a value of unity for the transmission coefficient K.[21b]

Table 3. Spectral parameters and $\Delta G^{\neq}_{Tc}$ values [kJ·mol^{-1}][a] for *E*, *Z* interconversion in pyran 2-imines **4**

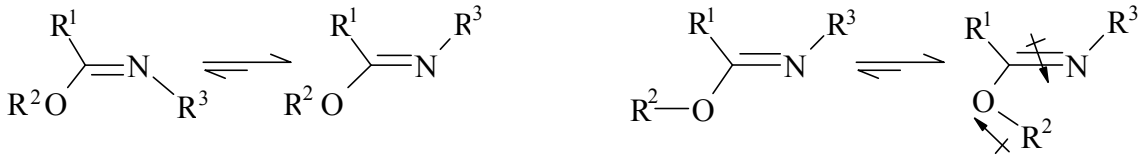
		H-3				H-5				4-Me			
Solv.	p_Z	δν [Hz]	T_c [K]	$\Delta G^{\neq}$ $E\rightarrow Z$	$Z\rightarrow E$	δν [Hz]	T_c [K]	$\Delta G^{\neq}$ $E\rightarrow Z$	$Z\rightarrow E$	δν [Hz]	T_c [K]	$\Delta G^{\neq}$ $E\rightarrow Z$	$Z\rightarrow E$
4a C_5D_5N	0.79	101	365	75.0	79.0	11	331	73.6	77.2				
C_2D_6SO	0.86	150	373	75.0	80.7								
4b C_5D_5N	0.73	74	358	74.1	77.0					38	348	73.5	76.4
C_2D_6SO	0.76									31	346	73.6	76.9
4d C_5D_5N	0.89					6.3	375	85.4	91.9				

[a] Experimental error range ±0.5

The data in Table 3 showed that $\Delta G^{\neq}$ measured at two different temperatures were quite close within experimental errors range, and also that it was not sensitive to changing the solvent from C_5D_5N to C_2D_6SO. The 4-R' substituent had negligible effect on $\Delta G^{\neq}$. However, the nitrogen substituent was found to have a significant effect: the barrier is higher by 11 kJ·mol^{-1} in the N-*i*Pr imine **4d** than in the N-Ph analog **4b**.

Discussion

The stereochemical analysis gave prevailing **4-*Z*** conformation by two independent procedures. The consistency of the data in the series is reassuring, particularly since the stereochemical analysis in opened-chain related systems was not devoid of controversy. Imidate esters **8** had been initially reported[22] as stable *Z*-isomers ($\Delta G^{\neq} > 23$ kcal·mol^{-1}), but later studies found much lower barriers for *E*, *Z* interconversion and established prevailing *E*-conformation.[23,24] This was explained by preference in antiperiplanar *E-ap* conformation, in which partial cancellation of dipoles occurs (Scheme 4). It is interesting to note that *E-ap* geometry was indeed found in imidates **8** by NOE experiments.[25] Obviously, this cannot be the driving force in the cyclic pyran 2-imines **4**.



Z - **8** *E* - **8** *E* - *sp* *E* - *ap*

Scheme 4

For explaining the prevalence of *Z*-**4** conformation, both electronical and steric factors are taken into account. The electrostatic repulsion between nitrogen and oxygen lone pairs should disfavour the *E*-conformer. The steric effect operates in the same sense, since the interference between the substituent R on nitrogen and the H-3 atom of the pyran ring disfavours also the *E*-conformer. Indeed, the molar fraction of the *E*-conformer in $CDCl_3$ was 0.25 in **4a** and 0.35 in **4b** when R = Ph, but decreased to 0 when R was as bulky as *t*Bu (**4c**). The aromatic ring may easily release the steric strain by torsion, shielding the 3-H atom as observed experimentally.

The free energy of activation $\Delta G^{\neq}$ of *E*, *Z*-interconversion in imines **4** decreased significanly when the substituent on nitrogen changed from alkyl to aryl, but presented negligible solvent and temperature effects (Table 3). These findings are in agreement with an "in plane" inversion (*sp* nitrogen) mechanism for interconversion.[26] The aromatic ring on nitrogen, orthogonal to the inversion plane, gives a better conjugation with the occupied *p* orbital in the transition state as compared to the conjugation with the occupied sp^2 orbital in the ground state, decreasing the interconversion barrier.

Finally, a comparison with topomerization of pyran 4-imines **5**, occurring by nitrogen inversion or a mechanism intermediate between inversion and rotation,[18] seems appropriate (barriers obtained in solvents of similar polarity are compared). For the N-phenyl pyran 4-imine **5** (R = Ph), the barrier in CD_3NO_2 was found to be 81.3 ± 0.5 kJ·mol^{-1}. This is quite close to the barrier for *Z*-*E* isomerization found for **4a** in DMSO-d_6 (80.7 ± 0.5 kJ·mol^{-1}) but higher than the barrier for the reversed *E*-*Z* process (75.0 ± 0.5 kJ·mol^{-1}). Since the difference between ground state and transition state in **5** and in *Z*-**4a** is the same, a destabilizing effect should operate in *E*-**4a** and the interorbital repulsion between non-bonding electrons on nitrogen and the endocyclic oxygen atom may well account for it.

Conclusions

The stereochemical analysis based on ^{1}H and ^{13}C NMR spectroscopy in the series of N-aryl (or alkyl) substituted 2*H*-pyran-2-imines **4a-e** established, by two independent procedures, prevalence of *Z*-conformation. The barriers $\Delta G^{\neq}_{Tc}$ determined by ^{1}H-DNMR are in agreement with a planar nitrogen inversion mechanism for *E*, *Z* interconversion. To our knowledge, this is the first stereochemical description of N-substituted pyran 2-imines.

Experimental Section

General Procedures. The NMR spectra were recorded with a Varian Gemini 300 BB instrument operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C. The chemical shifts are given in ppm, from TMS as internal standard. The temperature controller in the DNMR experiments was calibrated

against ethyleneglycol, the measurement accuracy being ± 2K. Preparation of compounds **4a-4d** were published earlier.[1]

***N*-[6-(1-Methylethyl)-4-phenyl-2*H*-pyran-2-ylidene]-2-propanamine** (**4e**)**.** 1.70 g (5 mmol) 2,6-Diisopropyl-4-phenylpyrylium perchlorate[27] (the synthesis of the tetrafluoroborate salt has been described earlier)[28] was shaken briefly with 1.04 g (15 mmol) hydroxylamine hydrochloride, 30 mL aqueous 0.5N NaOH and 50 mL diethyl ether. The ethereal layer was evaporated under vacuum. The residue (1.1 g) in 15 mL CCl_4 was treated dropwise with 0.3 mL (4 mmol) thionyl chloride in 5 mL CCl_4, under magnetic stirring and with cooling in ice-water bath. After removing the solvent, water was added and the mixture was extracted with diethyl ether. In the aqueous phase, hydroperchlorate of pyran-imine **4e** was precipitated with perchloric acid. The imine **4e** was obtained from hydroperchlorate by treatment with aqueous ammonia and extraction with diethyl ether.
Hydroperchlorate. m.p. 165-6°C (gl. acetic acid/ ethyl ether). Anal. Calcd. For $C_{17}H_{22}NClO_5$: C, 57.39; H, 6.23; N, 3.94; Cl, 9.96. Found: C, 57.24; H, 6.53; N, 4.21; Cl, 11.20.

Acknowledgments

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