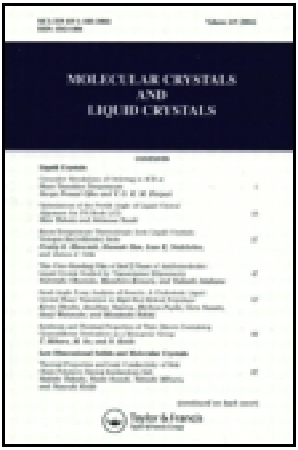

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The Enantiomers of Indolino Spiro Compounds. Barriers to Thermal Cleavage of Their C(sp^3)-O BOND*

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THE ENANTIOMERS OF INDOLINO SPIRO COMPOUNDS. BARRIERS TO THERMAL CLEAVAGE OF THEIR C(sp^3)-O BOND*

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Abstract The enantiomers of the title compounds were separated for the first time by liquid chromatography (LC) on optically active sorbents analytically or preparatively. They were characterized mainly by their retention factors and by circular dichroism. Barriers to thermal cleavage of the C(sp^3)-O bond were mainly determined by a combination of polarimetry and LC without preparative enrichment of enantiomers. These $\Delta G_1^{\neq}$-values (81.5 - 99.2 kJ/mol) are discussed with reference to substitution; it is concluded that the C-O bond in oxazines (Table IV, X = $\overline{N}$) is broken less easily than the one in pyrans (X = CH). These thermal enantiomerizations (Scheme 1) are examples of fast valence isomerizations.

INTRODUCTION

Indolino spiro compounds have been of some interest because of their thermochromism. Therefore, equilibria with the corresponding merocyanines $(I)_{kT}$ (Scheme 1) have been detected in many cases and enthalpy differences ΔH have been determined.[3,4] Photochromism of such compounds has found practical use for protection against light. Therefore, still more representatives of the above class of molecules are known for which merocyanines have been generated by irradiation and enthalpies of activation for the thermal re-formation of the spiro compounds (decoloration) have been measured.[3-5] However, the rate constants k_1 for the thermal generation of merocyanines[6-9] $(I)_{kT}$ (Scheme 1) and the corresponding barriers $\Delta G_1^{\neq}$ have not been reported in many cases. Therefore, the present work intends to measure such rate constants and the corresponding $\Delta G_1^{\neq}$-values of indolino spiro compounds[10,11] for the first time by *another* method, racemization of enantiomers (Scheme 1), although the latter are unknown. This approach had proven successful for other types of benzopyrans.[1,2,10-12]

SEPARATION AND CHARACTERIZATION OF THE ENANTIOMERS

Some of the racemic mixtures of the spiro compounds investigated were described, others were not. All of them were prepared according to known methods of synthesis[4,5,13] and characterized by all usual methods. The enantiomers were separated analytically by liquid chromatography (LC) on microcrystalline triacetylcellulose[14] (TAC) using MeOH or EtOH as eluents and a polarimeter[11] as a second detector. Chiroptical detection, contrary to the photometric one, indicates good *and* bad separations[15], the latter bringing about fused photometric peaks for the enantiomers. Therefore, the corresponding chromatograms and retention factors[14] k′, obtained on TAC and sometimes on further optically active sorbents, serve to characterize the enantiomers.[16] It will be shown below that the barriers $\Delta G_1^{\neq}$ to enantiomerization are lower than 100 kJ/mol in all cases, i.e. the half-lives of the enantiomers at room temperature are of the order of magnitude of minutes or shorter. For this reason and, in some cases, for the additional reason of bad separation, the *preparative* enrichment was successful only for two oxazines (Table I). However, circular dichroism (CD) data were accessible for the enantiomers of several other spiro compounds even without their preparative enrichment. This was accomplished by a combination[10,15,17] of CD and LC measurements, i.e. by on-line CD. Therefore, these CD results[16] contribute to the characterization of the enantiomers.

BARRIERS TO CLEAVAGE OF THE C(sp^3)-O BOND

In a similar way, the thermal racemizations, monitored by polarimetry, were either performed after preparative enrichment of enantiomers (off-line procedure) or by a combination[15] of polarimetry and LC (on-line procedure) without an enrichment. For two oxazines, rates were obtained by coalescence of ^{1}H NMR singlets of diastereotopic CH_3 groups on the indoline ring. Barriers $\Delta G_1^{\neq}$ (Tables II - IV) were computed from the rate constants. For 1 in EtOH the activation parameters $\Delta H_1^{\neq} = 103 \pm 2$ kJ mol^{-1} and $\Delta S_1^{\neq} = +24 \pm 5$ JK^{-1}mol^{-1} were determined in addition. The latter result was used in the calculation (Table IV) of the $\Delta G_1^{\neq}$-value for one temperature from the value for another one (although these were measured in $C_6D_5NO_2$, not EtOH).

The barriers in Tables II - IV and similar values[16] indicate some trends which apparently originate from stabilization or destabilization of the intermediate(s) $(I)_{kT}$ (Scheme 1) and the corresponding transition state by substituents. In the same way, the incorporation of an additional benzo ring into the benzopyran moiety seems to lower $\Delta G_1^{\neq}$ (cf. 8 in Table III and 10 in Table IV). On the other hand, there is no easy explanation for the increase of the barrier by about 12 kJ/mol upon comparison of the pyran 10 with the oxazine 1 (Table IV). The finding of $\Delta G_1^{\neq}$ = 81.5 kJ/mol for 10 in Table IV means that its half-life before thermal ring-opening at room temperature is of the order of 10s only. Therefore, the thermal enantiomerizations according to Scheme 1 represent further examples for fast valence isomerizations.

The barriers of indolinobenzopyran 8 and 2,2'-spirobi[2*H*-1-benzopyran] in Table III show that the indoline and the benzopyran systems apparently provide very similar stabilizations to the intermediate(s) in Scheme 1 and to the corresponding transition state.

For oxazine 1, Chu[13] gave the enthalpy of activation $\Delta H_2^{\neq}$ for formation of the $C(sp^3)$-O bond and the enthalpy difference ΔH for the equilibrium with $(I)_{kT}$ (Scheme 2). Within error limits, his findings fit our value of $\Delta H_1^{\neq} = 103 \pm 2$ kJ/mol for bond cleavage, thus showing that the results of thermal decoloration, thermochromic equilibrium and thermal enantiomerization are consistent.

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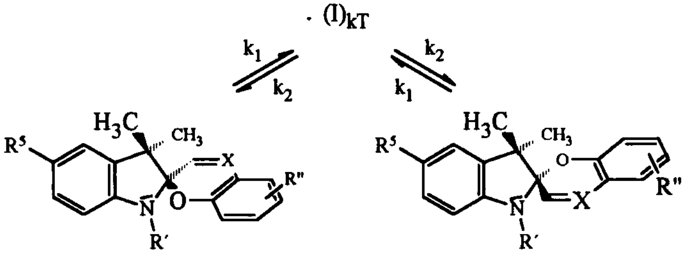
SCHEME 1 Thermal interconversion of enantiomers via intermediates(s) $(I)_{kT}$. k_1, k_2: Rate constants of cleavage and formation of the $C(sp^3)$-O bonds, respectively.



SCHEME 2 Cleavage and formation of the C(sp^3)-O bond of **1** (EtOH). The present (E)/(Z) isomer of intermediates $(I)_{h\nu}$ and $(I)_{kT}$ is preferred.[18] Further isomers and resonance structures are symbolized by corresponding signs. Top: Thermal bond formation ($\Delta H_2^{\neq}$ = 84 ± 5 kJ/mol)[13] after photochemical cleavage. Centre: Thermal equilibrium (ΔH = 22.7 ± 1.2 kJ/mol)[13] and thermal bond cleavage ($\Delta H_1^{\neq}$ = 103 ± 2 kJ/mol), the latter being measured by on-line racemization (see text).

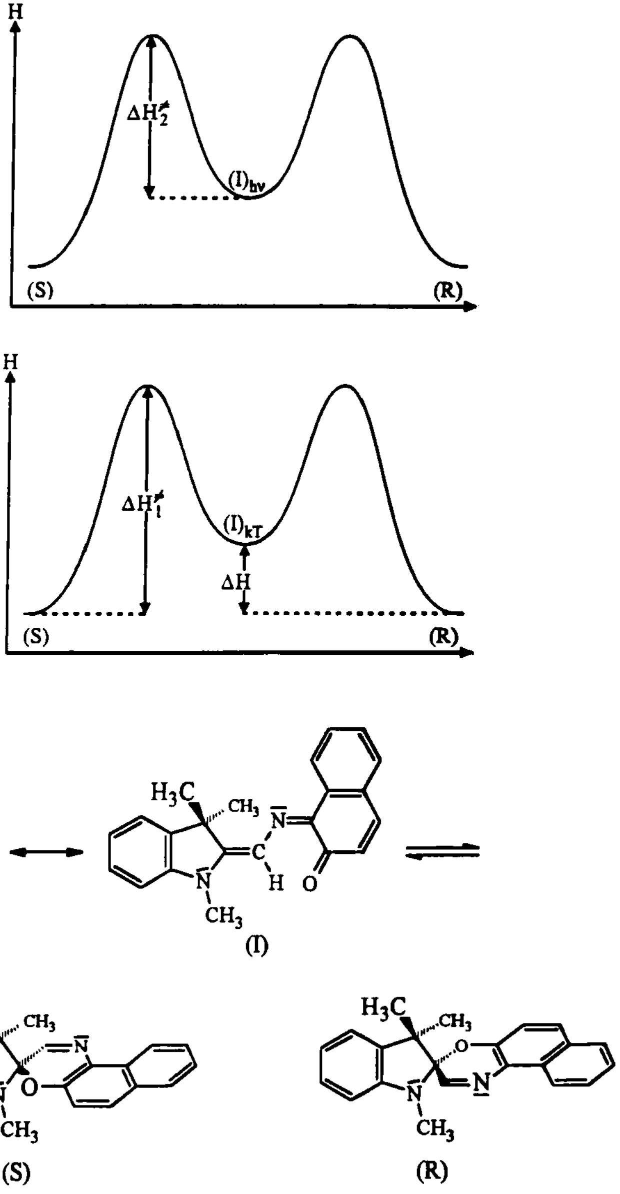
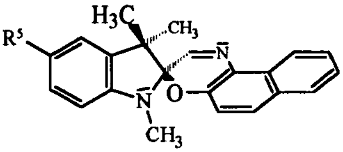


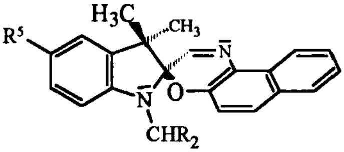
TABLE I Retention factors k' on triacetylcellulose (pressure 2 bar; EtOH for 1, MeOH for 2), enantiomeric purities P (± 2 %), melting points m and circular dichroism maxima (MeOH) for P = 100 %. Only *one* enantiomer shown.



	R^5	k'	P	m [°C]	$\Delta\varepsilon_{max}$ [l mol^{-1} cm^{-1}]			
					λ_{max} [nm]			
(+)-1	H	1.8	51	117-122.5	+32.0	+8.3	-6.8	+0.8
					235	285	323	363
(-)-1	H	1.0	72	118.5-123.5	a)			
(+)-2	F	1.3	85	159-165	+17.0	+10.1	-11.6	+0.9
					242	290	324	363
(-)-2	F	0.7	94	166-170	a)			

a) Practically identical with results of (+) enantiomer, except signs.

TABLE II Barriers to cleavage of the C(sp^3)-O bond, measured by on-line racemizations (see text).



	R^5	R	$\Delta G^{\neq}_{1}$, ± 0.2 kJ/mol	T °C	Solvent
3	H	Me	96.5	33.6	MeOH
1	H	H	95.1	33.5	EtOH
2	F	H	97.1	35.0	MeOH
4	Cl	H	95.7	34.9	EtOH
5	Br	H	94.9	33.5	MeOH
6	I	H	94.7	33.2	MeOH

TABLE III Barriers to cleavage of one C(sp^3)-O bond, measured by on-line or off-line racemizations (see text).

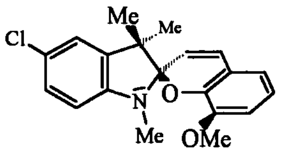
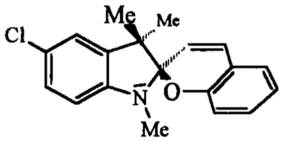
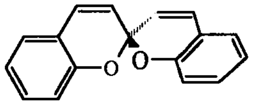
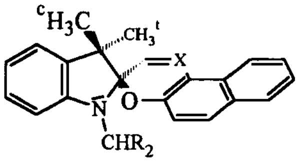
		$\Delta G_1^{\neq}$, ± 0.2 kJ/mol	T °C	Solvent Method
7		95.4	38.0	EtOH on line
8		99.2	41.7	EtOH on line
		99.0^2	45.0	MeOH off line

TABLE IV Barriers to cleavage of the C(sp^3)-O bond ($C_6D_5NO_2$).



	R	X	$\Delta G_1^{\neq}$ kJ/mol	T °C	Method
9	Me	CH	82.2 ± 0.7	115	a)
10	H	CH	81.5 ± 0.8	108	a)
1	H	$\overline{N}$	95.0 ± 0.2	30.0	b)
			93	108	c)

a) Coalescence of ^1H NMR CH_3 singlets at 80 MHz

b) Off-line racemization (see text)

c) $\Delta G^{\neq}$-value for 108°C was calculated from value measured at 30.0°C by use of $\Delta S^{\neq} = +24\ JK^{-1}mol^{-1}$.