ASYMMETRIC TRANSFORMATION. IV. FORMATION OF THE OPTICALLY ACTIVE CRYSTALS OF 1,4-BENZODIAZEPINOOXAZOLES

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Abstract— Two 1,4-benzodiazepinooxazoles which afforded optically active crystals consisting of one enantiomer were newly found as additional examples of the second-order asymmetric transformation which occurs between the enantiomers. All the optically active crystals of three 1,4-benzodiazepinooxazoles had the same molecular conformation and the same crystal structure.

In a previous paper,[1] we reported that 10-bromo-11b-(2-fluorophenyl)-2,3,7,11b-tetrahydrooxazolo[3,2-d][1,4]benzodiazepin-6(5H)-one(1) gave optically active crystals of one enantiomer from a methanol solution under achiral condition, and concluded that this phenomenon was the result of preferential crystallization accompanying the second-order asymmetric transformation.[2] Racemization studies on the optically active crystals of 1 revealed that 1,4-benzodiazepinooxazoles in protic solvents were always interconverted between the enantiomers by epimerization *via an iminium ion intermediate as shown in Figure 1. Very fast epimerization* occurred, especially in methanol.[3] Therefore, we synthesized some analogs of 1 and tried crystallization to investigate whether it is possible to find a new compound which similarly affords optically active crystals by second-order asymmetric transformation.

We are interested in how the fluorine atom at the 2 position of 1 functions in the formation of the optically active crystals of one enantiomer which accompanies the second-order asymmetric transformation. Therefore, two analogs, (2)and (3), which contained fluorine atom at the 2 position, were synthesized. Three analogs, (4), (5), and (6), in which fluorine is replaced by hydrogen or chlorine, were synthesized as reference compounds. The syntheses of these analogs were carried out by

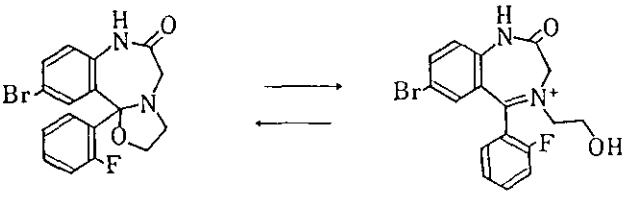

Figure 1. Epimerization of 1,4-Benzodiazepinooxazoles

the known method mentioned in the previous reports.[1,4]

Each compound was crystallized when the reaction mixture of the final step was allowed to stand at room temperature after refluxing for 15 to 20 h. Specific rotations of these crystals were measured in dioxane. Compounds (2) and (3) showed large specific rotations of +362° and -243°, but the other three compounds did not show optical activity. The results thus obtained are listed in Table I. Thus we newly found two more compounds which give optically active crystals among the 1,4-benzodiazepinooxazole analogs. Then the physicochemical properties of these two compounds, (2) and (3), were studied to compare with those of 1. Racemization rates of the optically active crystals of 2 and 3 were measured at 20°C in a 1:3 (v/v) mixture of methanol and ethyl acetate. The results are shown in Table II. Compound (2), which has a chlorine atom at the 10 position, showed a comparable racemization rate to 1, but 3, which has methyl, an electron donating substituent, at the 10 position had about ten times faster racemization rate than 1.

For compounds (4), (5), and (6), racemizations cannot be observed but the presence of the epimerization between enantiomers can be estimated from the pK_a values of 6.48 for 4 and 7.27 for 6, of which data were reported by Ikeda,[5] as acid base equilibrium constants of those analogs. The larger pK_a value corresponds to faster epimerization.

The crystal structures of 2 and 3 were determined by X-ray analyses of each optically active crystal. The crystal data of 1, 2 and 3 were the same as shown in Table III. This result shows that these three optically active crystals are isomorphous to each other. Therefore, 1, 2 and 3 have the same crystal structure and the same molecular conformation as shown in Figure 2.[4]

On the other hand, the optically inactive crystals of 6 were recrystallized from methanol at various temperatures and concentrations, but the same prismatic and optically inactive crystals were obtained in every case. X-Ray analysis of this crystal showed that it has a space group of P1 or $P\bar{1}$, and crystal data were as

Table I. Crystals of 1,4-Benzodiazepinooxazole Derivatives

	R_1	R_2	Yield(%)	mp(°C)	$[\alpha]_D^{20}$
1	Br	F	80	188-191	-326°
2	Cl	F	51	181-182	+362°
3	CH_3	F	52	172-174	-243°
4	Cl	H	58	175-176	0
5	Br	H	54	190-192	0
6	Cl	Cl	71	203-204	0

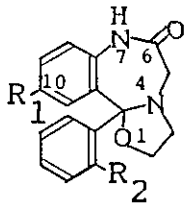

Table II. Comparison of the Rate Constant (k_{obs}) of Epimerization

	solvent system MeOH/dioxane	k_{obs} / min (20°C)
1	25 / 75 (v/v%)	1.1×10^{-3}
2	25 / 75	9.1×10^{-4}
3	25 / 75	1.1×10^{-2}

Table III. Crystal Data of the Optically Active Crystals

	R_1	a	b	c(Å)	Space Group	Z
1	Br	10.333(3)	7.209(2)	21.286(6)	$P2_12_12_1$	4
2	Cl	10.315(3)	7.231(2)	20.778(6)	$P2_12_12_1$	4
3	CH_3	10.205(3)	7.180(2)	21.399(7)	$P2_12_12_1$	4

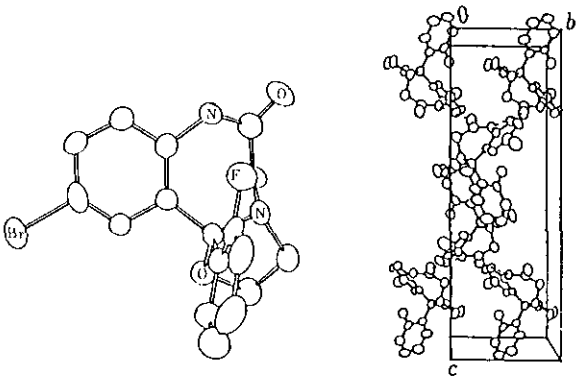

Figure 2. The Molecular Structure and the Molecular Packing for 1

follows: a=17.109(5), b=15.211(3), c=12.724(3)Å, α=106.00(2), β=100.14(2), γ=81.56(2)°, U=3116.5Å^3, Z=8. The cd spectrum of this crystal indicated no Cotton effect, although the optically active crystal of 1 having R or S configuration respectively showed the opposite Cotton effect. Therefore, this crystal must belong to the space group of $P\bar{1}$ which has a symmetric center. The crystal of 6 was determined to be a racemate, moreover, this racemate had a quite different crystal structure from either of the two racemates of polymorphous crystals of 1.[4] The relationship between the function of the fluorine atom in compounds (1), (2), and (3), and identity of the preferred conformation of these three enantiomers in each optically active crystal requires further investigation.

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