Upon DNP-aromatic Rule. Effect of Chromophore Exchange on the CD Spectra of *N*-DNP-arylalkylamines

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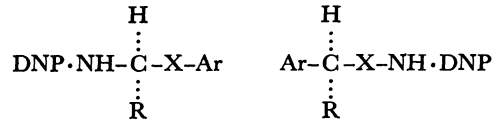
Synopsis. CD spectra of the analogs of aromatic DNP-α-amino acids and the related *N*-DNP-arylalkylamines, in which the positions of the two chromophoric groups were exchanged with each other, were studied. The analogs, in which the DNP-amino group is separated from the asymmetric carbon, did not show any marked Cotton effect near 400 nm, indicating the importance of direct attachment of the DNP–NH group to the chiral carbon atom for showing the characteristic CD spectra of *N*-DNP-aromatic α-amino acids.

Chiroptical properties of 2,4-dinitrophenyl (DNP) derivatives of aromatic α-amino acids and related compounds were studied extensively[1-6] and DNP-aromatic rule was proposed.[3] According to the rule the sign of $[\theta]_{\approx 400}$ is negative for the compounds of the formula **1**, where Ar and R are an aromatic and a nonaromatic groups, respectively. The symbol X represents a methylene chain, in which a hetero atom or such a group as ester, amide, *etc.* can be included.



1 **2**

(for Ar, R, and X see Table 1)

As an attempt to investigate the basis of the rule, DNP-amino compounds **2**, which are the chromophore exchanged analogs of **1**, were prepared and their CD spectra were compared. Assuming that the Cotton effects are due to the exciton coupling between the two chromophores,[7] essentially same spectra are expected for the compounds having the same relative orientation of the electric transition moments. Thus, if the transition moments of both chromophores have similar orientation relative to the attaching bond and exchange of the chromophoric groups doesn't cause significant change of molecular conformation, similar CD spectra can be expected for each pairs of **1** and **2**.

CD spectra of **1a—g** and **2a—g** measured in methanol are summarized in Table 1. All of the type **1** compounds exhibited distinctly negative Cotton effect around 400 nm reflecting the absolute configuration of the chiral center as stated by DNP-aromatic rule. In all the pairs examined, however, the molecular ellipticities of **2** at 400 nm were much weaker than those of **1**, and apparently no simple relation was found between the sign of the Cotton effect and the absolute configuration. Since the assumption of similar molecular conformation of **1** and **2** seems reasonable, the unexpected low $[\theta]_{\approx 400}$ values of **2** are attributed to the increased freedom of rotation around the DNPNH–C bond in **2** compared to that in **1**, which results in different average relative orientation of the transition moment. Direct attachment of DNP–NH to the asymmetric carbon restricts rotation around that bond as confirmed by the conformational energy calculation of DNP-L-alanine using ECEPP program;[8] *i.e.*, only the values −60°——85° and

TABLE 1. CD SPECTRAL DATA OF **1** AND **2** RECORDED IN METHANOL

	Ar	R	X	Molecular ellipticity($[\theta]\times 10^{-2}$) and wavelength(λ/nm) in parentheses[a]
1a	Ph	CO_2H	CH_2	−91(410),0(363),+74(334),+21(296),+46(270),+23(254)
2a	Ph	CH_3	CH_2	−19(415sh),−47(355),0(290)
1b	$PhCO_2$	CH_3	CH_2	−61(400),0(347),+23(325),+9(300),+170(238)
2b	$PhCO_2$	CH_3	CH_2	−4(420sh),−78(343),0(287),+22(268),0(253),−6(247),0(243)
1c	PhCONH	CH_3	CH_2	−97(409),−70(370sh),0(300),+45(372),+166(238)
2c	PhCONH	CH_3	CH_2	+10(415),0(390),−91(345),0(275),−115(243)
1d	PhCONH	CO_2H	$(CH_2)_3$	−59(405),0(341),+11(324),+3(308),+75(264)
2d	PhCONH	CO_2H	$(CH_2)_3$	+8(415),0(380),−16(345),0(280)
1e	PhCONH	CO_2H	$(CH_2)_4$	−42(408),0(352),+22(332),0(300),+28(265),0(244)
2e	PhCONH	CO_2H	$(CH_2)_4$	+11(420),0(380),−8(340),0(300),−8(275)
1f	p-$NO_2C_6H_4NHCO$	CH_3	$CONHCH_2$	−112(395),0(355),+82(337),0(313),−13(300),0(287),+6(280),0(270)
2f	p-$NO_2C_6H_4NHCO$	CH_3	$NHCOCH_2$	−43(400),−40(386),−42(375),0(348),+37(325),0(302),−25(275)
1g	p-$NO_2C_6H_4NHCO$	CO_2H	$(CH_2)_2$	−108(402),0(371),+202(432),0(319),−20(306),0(292),+13(275),0(260)
2g	p-$NO_2C_6H_4NHCO$	$NHCO_2$-$C(CH_3)_3$	$(CH_2)_3$	−4(420sh),−40(345),0(313),+2(295)

a) sh: Shoulder. The underlined values are those of $[\theta]^{max}$ near 400 nm.

$-145°$——$-165°$ are allowed for ϕ.[9] Thus, much smaller ellipticities of **2** compared to those of **1** were deduced to be due to the loss of restricted rotation of DNP–NH group caused by the presence of intervening achiral chain X between the DNP–NH group and the chiral center.

It is noteworthy that introduction of just one methylene between the DNP–NH and asymmetric carbon of (*S*)-DNP-NHCH(CH_3)Ph ($[\theta]_{406}+16200$) affords **2a** possessing very low $[\theta]_{400}$ value. Insertion of a methylene chain [$(CH_2)_n$, $n=1$—5] between the asymmetric carbon and the phenyl group of L-DNP-NHCH(CO_2H)-Ph doesn't cause marked change of the CD spectra.[1,3]

Experimental

Melting points were uncorrected. Compounds **1a**—**e** and **1g** were described in Ref. 3. The DNP derivatives **1a**, **1f**, **2a**, and **2g** were prepared in enantiomeric form. 2,4-Dinitrophenylations were performed with the procedure of Sanger[10] unless otherwise stated. All the PMR spectra (Hitachi R-24 spectrometer; $CDCl_3$, acetone-d_6, or DMSO-d_6) of the compounds synthesized were consistent with the assigned structures.

*(2R)-N-DNP-2-phenylpropylamine (Enantiomer of **2a**).* Dinitrophenylation of 404 mg (1 mmol) of (2*R*)-2-phenylpropylamine L-malate ($[\alpha]_D^{22}$ +21.1°, *c* 4.1, H_2O)[11] afforded enantiomer of **1a** (195 mg): orange crystals from benzene; mp 89—90 °C. Found: C, 59.30; H, 4.94; N, 13.83%. Calcd for $C_{15}H_{15}N_3O_4$: C, 59.79; H, 5.02; N, 13.95%.

*(2R)-N-DNP-O-benzoyl-1-amino-2-propanol (**2b**).* Dinitrophenylation of 112 mg (1 mmol) of (2*R*)-1-amino-2-propanol ($[\alpha]_D^{22}$ −32.8°, *c* 2, CH_3OH)[12] afforded *N*-DNP derivative (80 mg, mp 94—96 °C) as yellow needles from benzene–hexane. This compound was benzoylated with benzoyl chloride–pyridine to give **2b** (73 mg) as yellow powder from benzene: mp 131—132 °C. Found: C, 55.10; H, 4.35; N, 12.10%. Calcd for $C_{16}H_{15}N_3O_6\cdot(1/4)H_2O$: C, 54.94; H, 4.47; N, 12.01%.

*(2R)-N^1-DNP-N^2-benzoyl-1,2-propanediamine (**2c**).* To a stirred mixture of 0.75 g (2 mmol) of (2*R*)-1,2-propanediamine L-tartrate ($[\alpha]_D^{23}$ +21.2°, *c* 1.63, H_2O) and $NaHCO_3$ (0.6 g, 7 mmol) in H_2O were added 1-fluoro-2,4-dinitrobenzene (0.37 g, 2 mmol) in acetone and then benzoyl chloride (0.47 ml, 4 mmol) and $NaHCO_3$ (1 g, 12 mmol). The main product **2c** was isolated using preparative TLC (SiO_2, developed 7 times with $CHCl_3$) as yellow powder (47 mg), which had slightly higher R_f value than that of the isomer **1c**.[3]

*N^δ-DNP-N^α-benzoyl-L-ornithine (**2d**).* N^δ-DNP-N^α-*t*-butoxycarbonyl-L-ornithine (mp 65—72 °C; 100 mg, 0.25 mmol), prepared from N^α-*t*-butoxycarbonyl-L-ornithine, was treated with trifluoroacetic acid and was benzoylated with benzoyl chloride (0.06 cm^3, 0.5 mmol) and NaOH to afford **2d** (78 mg) as yellow powder from methanol–H_2O: mp 181—183 °C. Found: C, 53.36; H, 4.67; N, 13.41%. Calcd for $C_{18}H_{18}N_4O_7\cdot(1/4)H_2O$: C, 53.14; H, 4.58; N, 13.77%.

*N^ϵ-DNP-N^α-benzoyl-L-lysine (**2e**).* N^α-Benzoyl-L-lysine (125 mg, 0.5 mmol) was dinitrophenylated to give **2e** (210 mg) as yellow crystals from ethyl acetate–hexane: mp 110—113 °C. Found: C, 54.23; H, 4.89; N, 13.35%. Calcd for $C_{19}H_{20}N_4O_7\cdot(1/4)H_2O$: C, 54.22; H, 4.91; N, 13.31%.

*DNP-L-alanylglycine p-Nitroanilide (Enantiomer of **1f**).* DNP-L-alanine *N*-hydroxysuccinimide ester (mp 148—152 °C; 260 mg, 0.73 mmol) and trifluoroacetate of glycine *p*-nitroanilide, prepared from *t*-butoxycarbonylglycine *p*-nitroanilide (mp 180—181 °C; 200 mg, 0.67 mmol), were allowed to react in DMF to give enantiomer of **1f** (180 mg) as yellow fine needles from acetone: mp 292—295 °C. Found: C, 47.47; H, 3.96; N, 19.27%. Calcd for $C_{17}H_{16}N_6O_8$: C, 47.22; H, 3.73, N, 19.44%.

*DNP-glycyl-L-alanine p-Nitroanilide (**2f**).* Coupling reaction of *t*-butoxycarbonylglycine (117 mg, 0.67 mmol) and L-alanine *p*-nitroanilide trifluoroacetate, prepared from *t*-butoxycarbonyl-L-alanine *p*-nitroanilide (mp 130—135 °C; 103 mg, 0.33 mmol), using dicyclohexylcarbodiimide (83 mg, 0.4 mmol) in DMF afforded *t*-butoxycarbonylglycyl-L-alanine *p*-nitroanilide (90 mg) as an oil. This compound was treated with trifluoroacetic acid and dinitrophenylated to give **2f** (90 mg) as yellow crystals from ethyl acetate: mp 224—227 °C (decomp). Found: C, 47.03; H, 3.69; N, 19.23%. Calcd for $C_{17}H_{16}N_6O_8$: C, 47.22; H, 3.73; N, 19.44%.

*N^δ-DNP-N^α-t-butoxycarbonyl-L-ornithin p-Nitroanilide (Enantiomer of **2g**).* N^δ-DNP-N^α-*t*-butoxycarbonyl-L-ornithine (120 mg, 0.3 mmol), *p*-nitroaniline (137 mg, 1 mmol), and dicyclohexylcarbodiimide (103 mg, 0.5 mmol) in THF afforded enantiomer of **2g**, which was purified by preparative TLC (SiO_2, developed 3 times with $CHCl_3$): yellow powder (7 mg); mp 190—200 °C (decomp).

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