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Single Enantiomer, Chiral Donor–Acceptor Metal Complexes from Bisoxazoline Pseudoracemates

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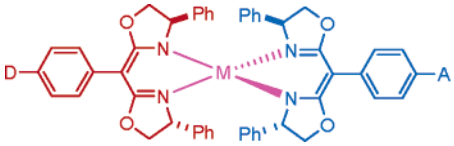
ABSTRACT



Single enantiomer, chiral donor–acceptor metal complexes were synthesized via the self-discriminating zinc(II) complexation of a pseudoracemic mixture of donor/acceptor-substituted bisoxazoline derivatives.

We recently reported the multicomponent self-assembly of neutral, heteroleptic (box)$_2$Zn complexes directed via chiral self-discrimination of enantiomeric bisoxazoline (box) ligands.[1] Combining a racemic mixture of phenyl-substituted box ligands (*R*,*R*)-**1** and (*S*,*S*)-**1** with Zn(OAc)$_2$ could afford three complexes: the heterochiral complex (*RR*,*SS*)-**2** (i.e., the product of chiral self-discrimination) and the two homochiral (*RR*,*RR*)- and (*SS*,*SS*)-complexes (i.e., the products of chiral self-recognition). We find that steric interactions between the pendant aryl groups lead to a strong preference for the tetrahedral (*RR*,*SS*)-**2** complex under reaction conditions that allow rapid equilibration. X-ray quality crystals of (*RR*,*SS*)-**2** were grown from CH$_2$Cl$_2$/EtOH solution by slow evaporation; the crystal structure is shown in Figure 1.

The self-discriminating zinc(II) complexation of a box ligand racemate can be extended to pseudoracemates, that is, pairs of (*R*,*R*)- and (*S*,*S*)-box derivatives bearing different substituents, thereby providing a general strategy for coupling two unique components via the formation of a chiral zinc complex.[2] Metal−organic complexes comprising electron donor, π-bridge, and acceptor (D−π−A) subunits have attracted much attention in large measure because of their nonlinear optical properties[3] and potential applications in electrooptics and molecular photonics.[4] Pseudoenantiomeric donor/acceptor-substituted aryl-substituted box ligands, such as **3** and **4**, have the potential to form single enantiomer, chiral donor−acceptor complexes (i.e., DA complex (*RR*,*SS*)-**5**) in which the metal center is intended to function as a π-bridge (Figure 2).

A series of chiral monosubstituted aryl-box derivatives bearing electron-donating and -accepting groups were synthesized. Although a large number of chiral box derivatives have been prepared for use as chiral ligands in asymmetric catalysis,[5] other than the commercially available cyano-

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[1] Takacs, J. M.; Hrvatin, P. M.; Atkins, J. M.; Reddy, D. S.; Clark, J. L. *New J. Chem.* **2005**, *29*, 263−265.

[2] The combinatorial synthesis of chiral self-assembled ligands for asymmetric catalysis via the box-directed coupling of bifunctional ligands is an ongoing application of this strategy. See: Takacs, J. M.; Reddy, D. S.; Moteki, S. A.; Wu, D.; Palencia, H. *J. Am. Chem. Soc.* **2004**, *126*, 4494−4495. Takacs, J. M.; Chaiseeda, K.; Moteki, S. A.; Reddy, D. S.; Wu, D.; Chandra, K. *Pure Appl. Chem.* **2006**, *78*, 501−509.

[3] Long, N. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 21−38. Di Bella, S. *Chem. Soc. Rev.* **2001**, *30*, 355−366. de la Torre, G.; Vazquez, P.; Agullo-Lopez, F.; Torres, T. *Chem. Rev.* **2004**, *104*, 3723−3750.

[4] Coe, B.; Curati, N. *Comments Inorg. Chem.* **2004**, *25*, 147−184.

[5] Rechavi, D.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 3467−3493.

10.1021/ol060836s CCC: $33.50

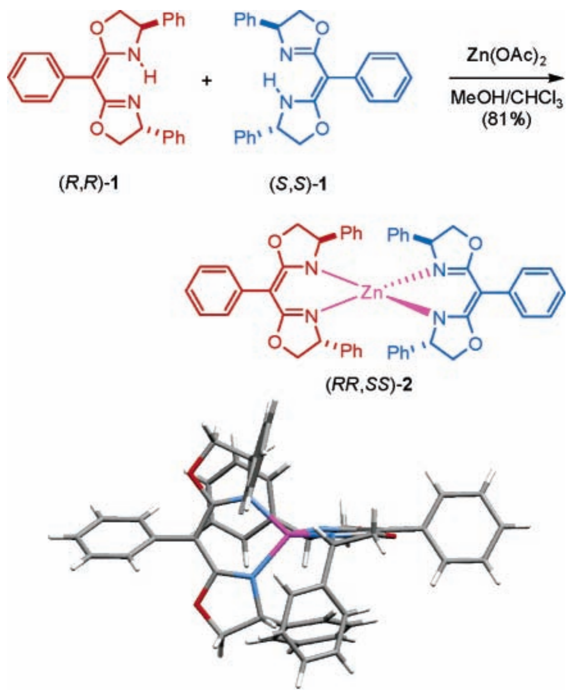


Figure 1. Preparation and crystal structure of (*RR*,*SS*)-**2**.

substituted derivative **6**,[6] relatively few chiral monoalkyl-substituted box derivatives (i.e., **7**) are known;[7] chiral monoaryl-substituted derivatives **8** have not been reported previously.

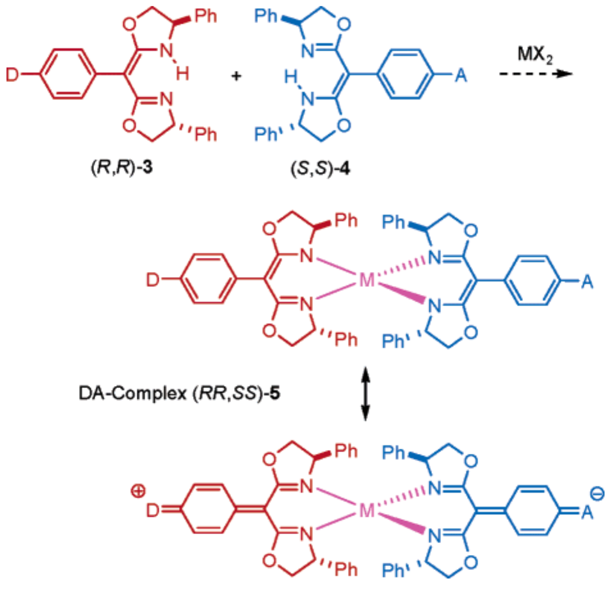
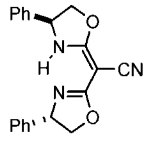


Figure 2. Chirality directed self-assembly of chiral (noncentrosymmetric) DA complexes, i.e., (*RR*,*SS*)-**5**.

A direct approach to **8**, palladium-catalyzed arylation of 2,2′-methylenebis[(4*S*)-4-phenyl-2-oxazoline] (i.e., **7**, R = Ph, R^1 = H), was fruitless; thus, the alternative route outlined in Scheme 1 was pursued. Palladium-catalyzed coupling of donor/acceptor-substituted aryl halides (i.e., **9**) with sodium malononitrile gives ready access to a variety of aryl-substituted malononitriles **10**.[8] The well-known ZnCl$_2$-catalyzed condensation of a nitrile with an amino alcohol has been used to prepare a variety of chiral oxazoline and box derivatives.[9] Adapting this method to the reaction of arylmalononitriles proved problematic initially, because the zinc complex **11** precipitated from solution under the reaction conditions, removing the Lewis acid catalyst. However, use



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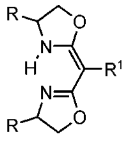

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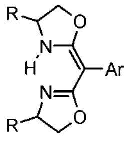

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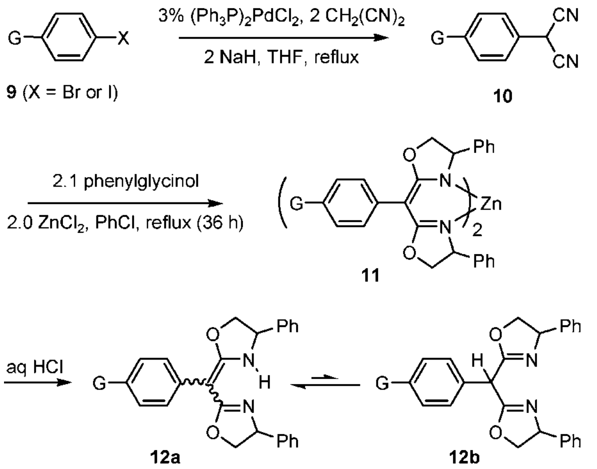
Scheme 1. Preparation of Donor/Acceptor-Substituted Box Derivatives **11** and **12**



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(6) Corey, E. J.; Wang, Z. *Tetrahedron Lett.* **1993**, *34*, 4001−4004. Kwak, Y.-S.; Corey, E. J. *Org. Lett.* **2004**, *6*, 3385−3388. Choi, H.-W.; Demeke, D.; Kang, F.-A.; Kishi, Y.; Nakajima, K.; Nowak, P.; Wan, Z.-K.; Xie, C. *Pure Appl. Chem.* **2003**, *75*, 1−17. Ward, D. E.; Sales, M.; Hrapchak, M. J. *Can. J. Chem.* **2001**, *79*, 1775−1785.

(7) Dagorne, S.; Bellemin-Laponnaz, S.; Welter, R. *Organometallics* **2004**, *23*, 3053−3061. Bayardon, J.; Sinou, D. *J. Org. Chem.* **2004**, *69*, 3121−3128. Zhou, J.; Ye, M.-C.; Tang, Y. *J. Comb. Chem.* **2004**, *6*, 301−304. Zhou, J.; Tang, Y. *Chem. Commun.* **2004**, 432−433. Bourguignon, J.; Bremberg, U.; Dupas, G.; Hallman, K.; Hagberg, L.; Hortala, L.; Levacher, V.; Lutsenko, S.; Macedo, E.; Moberg, C.; Queguiner, G.; Rahm, F. *Tetrahedron* **2003**, *59*, 9583−9589. Sibi, M. P.; Chen, J. *Org. Lett.* **2002**, *4*, 2933−2936. Bellemin-Laponnaz, S.; Gade, L. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 3473−3475. Burguete, M. I.; Fraile, J. M.; Garcia, J. I.; Garcia-Verdugo, E.; Herrerias, C. I.; Luis, S. V.; Mayoral, J. A. *J. Org. Chem.* **2001**, *66*, 8893−8901. Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F. *Eur. J. Org. Chem.* **2001**, 1045−1048. Denmark, S. E.; Stiff, C. M. *J. Org. Chem.* **2000**, *65*, 5875−5878. Schulze, V.; Hoffmann, R. W. *Chem.−Eur. J.* **1999**, *5*, 337−344.

(8) Uno, M.; Seto, K.; Masuda, M.; Ueda, W.; Takahashi, S. *Tetrahedron Lett.* **1985**, *26*, 1553−1556. Gao, C.; Tao, X.; Qian, Y.; Huang, J. *Chem. Commun.* **2003**, 1444−1445 and references therein.

(9) Bolm, C.; Weickhardt, K.; Zehnder, M.; Ranff, T. *Chem. Ber.* **1991**, *124*, 1173−1180. Makarycheva-Mikhailova, A. V.; Kukushkin, V. Y.; Nazarov, A. A.; Garnovskii, D. A.; Pombeiro, A. J. L.; Haukka, M.; Keppler, B. K.; Galanski, M. *Inorg. Chem.* **2003**, *42*, 2805−2813 and references therein.

of efficient stirring and excess of $ZnCl_2$ was sufficient to overcome this difficulty. After aqueous workup, complex **11** was isolated by precipitation from $CHCl_3$ with hexanes or by chromatography. Despite the initial difficulties, good yields of complex **11** were generally obtained (Table 1).

Table 1. Preparation of Donor/Acceptor-Substituted Box Derivatives **10** and **11** via the Route in Scheme 1

entry	G	X	**10** (%)	**11** (%)	configuration
1	H	I	83	88	(*RR*,*RR*)
2	H	I	83	88	(*SS*,*SS*)
3	MeO	Br	42	92	(*RR*,*RR*)
4	TBSO	Br	50	88	(*RR*,*RR*)
5	Et_2N	I	71	59	(*RR*,*RR*)
6	$CO_2{}^nBu$	I	84	98	(*SS*,*SS*)

Unlike the phenyl-substituted box complex (*RR*,*SS*)-**2** or the proposed DA complexes (*RR*,*SS*)-**5**, the isolated homochiral complex **11** has two identical box subunits bound to zinc. Although it has been noted that neutral zinc(II) complexes form more readily for electron-poor chelating ligands,[10] the homochiral complexes **11**, bearing either donors or acceptors, are accessible. Although the homochiral complexes are thermodynamically less stable than the corresponding heterochiral complexes, they are nonetheless quite robust. For example, **11** survives the extractive workup and chromatography on silica used in its isolation, and the TBS ether **11** (G = TBSO) is readily desilylated (TBAF, THF, 0 °C, 72%) to the corresponding phenol derivative **11** (G = OH). The homochiral complexes themselves can be used directly to prepare the desired donor−acceptor complexes (vide infra). In some cases, zinc can be removed by treating with dilute aqueous HCl, although this is accompanied by partial ligand hydrolysis. In solution, the free aryl-substituted box derivative **12** exists as a tautomeric mixture favoring tautomer **12a** over **12b**.

(4-Nitrophenyl)malononitrile (**13**)[11] is easily prepared via nucleophilic aromatic substitution. However, its $ZnCl_2$-promoted reaction with (*S*)-phenylglycinol proceeds only to the stage where one dihydrooxazole ring forms (i.e., **14**, Scheme 2). Finely ground KOH in pyridine[12] promotes substitution of 4-fluoronitrobenzene (**15**) with 2,2′-methylenebis[(4*S*)-4-phenyl-2-oxazoline] to give (*S*,*S*)-**16** as a red solid (65% yield).

Having prepared a series of donor-substituted aryl-box derivatives (*RR*,*RR*)-**11** (G = OMe, OTBS, OH, and NEt_2) and the stereochemically complementary acceptor-substituted aryl-box derivatives, (*SS*,*SS*)-**11** (G = $CO_2{}^nBu$) and (*S*,*S*)-**16**, as well as having purchased the commercially available cyano-substituted box (*S*,*S*)-**6**, we prepared a series of DA complexes (*RR*,*SS*)-**5a**−**f** (M = Zn) by combining the requisite pseudoracemates with $Zn(OAc)_2$ (Table 2). Complementary pairs of (*RR*,*RR*)- and (*SS*,*SS*)-homochiral $(box)_2Zn$ complexes disproportionate rapidly in protic solution to give the thermodynamically favored (*RR*,*SS*)-combination.[1] For example, the combination of (*RR*,*RR*)-**11** (G = NEt_2) with (*SS*,*SS*)-**11** (G = $CO_2{}^nBu$) gives zinc complex (*RR*,*SS*)-**5b** (D = Et_2N, A = $CO_2{}^nBu$). Although the box subunits used to direct complex formation are of opposite chirality, the donor−acceptor complexes (*RR*,*SS*)-**5a**−**f** are chiral and single enantiomers. For example, diethylaminophenylnitrophenyl DA complex (*RR*,*SS*)-**5e** exhibits a strong optical rotation, $[\alpha]^{589}{}_{D} = -346°$ ($c = 0.5$, $CHCl_3$).

Scheme 2. Preparation of the *para*-Nitro Derivative (*S*,*S*)-**16**

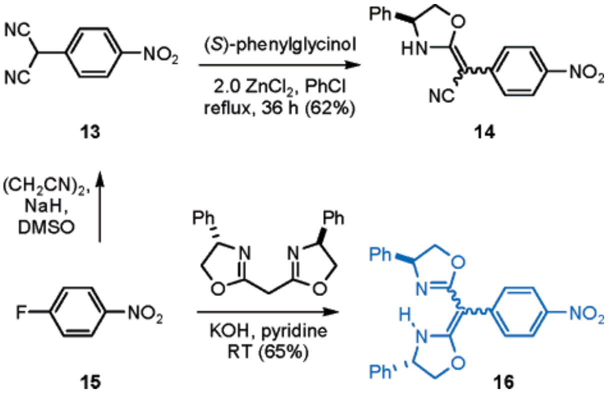

Table 2. Preparation of Zn(II) DA Complexes (*RR*,*SS*)-**5a**−**f** and the Donor and Acceptor Reference Complexes (*RR*,*SS*)-**5g**,**h**

entry	**5** (M = Zn)	D	A	yield (%)[a]
1	**5a**	TBSO	$CO_2{}^nBu$	67
2	**5b**	Et_2N	$CO_2{}^nBu$	99
3	**5c**	HO	NO_2	97
4	**5d**	MeO	NO_2	53
5	**5e**	Et_2N	NO_2	98
6	**5f**	Et_2N	CN	97
7	**5g**	Et_2N	Et_2N	82
8	**5h**	NO_2	NO_2	89

[a] Isolated yield after chromatography on silica (0−2% gradient of MeOH in $CHCl_3$).

Figure 3 shows the UV/visible spectra of (*RR*,*SS*)-**5e** and the symmetric diamino and dinitro complexes (*RR*,*SS*)-**5g** and (*RR*,*SS*)-**5h**. The latter were prepared from racemic mixtures of **11** (G = NEt_2) and **11** (G = NO_2), respectively (Table 2, entries 7 and 8). The spectrum of the Et_2N/NO_2 DA complex (*RR*,*SS*)-**5e** exhibits the expected nitroaromatic transition band at roughly half the intensity of (*RR*,*SS*)-**5h**, and the remainder of the spectrum in large part resembles a sum of the two individual ligand absorption bands. However, the slightly increased absorption intensity at the long wavelength edge in the DA complex suggests a weak CT transition. The weakness of the putative CT transition suggests that ligand geometry and the filled d-orbital set of

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(10) Abbotto, A.; Bradamante, S.; Facchetti, A.; Pagani, G. A. *J. Org. Chem.* **2002**, *67*, 5753−5772.

(11) Suzuki, H.; Koide, H.; Ogawa, T. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 501−504.

(12) Leader, H.; Smejkal, R. M.; Payne, C. S.; Padilla, F. N.; Doctor, B. P.; Gordon, R. K.; Chiang, P. K. *J. Med. Chem.* **1989**, *32*, 1522−1528.

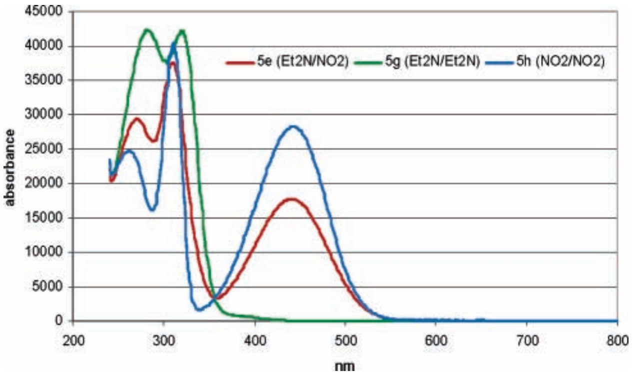

Figure 3. UV/vis spectra (240−800 nm) of DA complex **5e** (Et_2N/NO_2) and complexes **5g** (Et_2N/Et_2N) and **5h** (NO_2/NO_2).

the zinc ion lead to weak coupling of the aromatic donor and acceptor orbitals.

Attempts were made to crystallize several of the DA complexes; however, only the crystals of (*RR*,*SS*)-**5f** (Et_2N/CN) gave a solvable diffraction pattern (Figure 4). The unit cell consists of four complexes, each radiating out from the center of the cell. The structural features of (*RR*,*SS*)-**5f** are largely consistent with those found for simpler complexes. For example, the bond lengths and angles within the aminophenyl-substituted box subunit are much like those of the phenyl derivative (*RR*,*SS*)-**2**, and those for the cyano-substituted box subunit are similar to those reported for a related cyano-substituted semicorrin complex.[13] A slightly larger N−Zn−N bite angle is seen for the aminophenyl-substituted box subunit (93.85°) compared to the cyano-substituted box subunit (91.94°). In addition, the N−Zn bond lengths differ slightly for the two box derivatives; those for the aminophenyl-substituted box are slightly shorter. The angle defined by the central carbon of each box subunit and the zinc deviates about 10° from linear, and one of the dihydrooxazole rings in each ligand exhibits some disorder, indicating that these nonplanar rings have some conformational flexibility in the crystal.

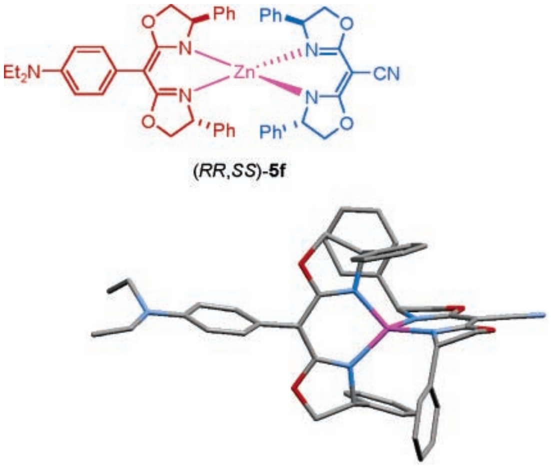

Figure 4. Crystal structure of DA complex (*RR*,*SS*)-**5f**.

Perhaps the most notable feature in the crystal structure of (*RR*,*SS*)-**5f** is that the aminophenyl ring is essentially orthogonal to the box π-system. The relevant dihedral angle is 96.96° indicating poor overlap in the ground state. Zn(II)-induced ground-state π-deconjugation has also been observed in *N*,*N*-bis(2-pyridyl)amino-substituted arenes.[14] Nonetheless, close contacts between the 4-(diethylamino)phenyl ring and an adjacent phenyl substituent within the crystal suggest packing forces may also play a role in the crystal structure. Furthermore, ground- and excited-state overlap are modulated by conformational dynamics, and overlap in the excited charge-transfer state is expected to increase.[15]

In summary, the self-discriminating zinc(II) complexation of a pseudoracemic mixture of substituted-box derivatives was used to prepare a series of single enantiomer, chiral DA complexes (*RR*,*SS*)-**5a**−**f**. The initial results suggest DA coupling is weak in these zinc complexes.[16] Further study of their excited-state and solid-state properties and the preparation of related DA complexes incorporating other metal ions are in progress.

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Supporting Information Available: Procedures, spectral data, and cif files. This material is available free of charge via the Internet at http://pubs.acs.org.

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[13] Saalfrank, R. W.; Struck, O.; Peters, K.; Georg von Schnering, H. *Z. Naturforsch., B: Chem. Sci.* **1994**, *49*, 1415−1424.

[14] Yang, J.-S.; Lin, Y.-D.; Lin, Y.-H.; Liao, F.-L. *J. Org. Chem.* **2004**, *69*, 3517−3525.

[15] Lin, V. S. Y.; Therien, M. J. *Chem.*−*Eur. J.* **1996**, *1*, 645−651.

[16] We appreciate the suggestion made by a reviewer that donor/acceptor interaction may contribute to the selective formation of (*RR*,*SS*)-DA complexes. However, we find that acid-catalyzed equilibration of an equimolar mixture of (*RR*,*SS*)-**5g** and (*RR*,*SS*)-**5h** (trace HOAc in $CDCl_3$) leads to a near statistical 2.7:1:1 mixture of DA complex (*RR*,*SS*)-**5e** and the two starting complexes, again suggesting that DA interaction in the ground state is weak.