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Chiral Action at a Distance: Remote Substituent Effects on the Optical Activity of Calyculins A and B

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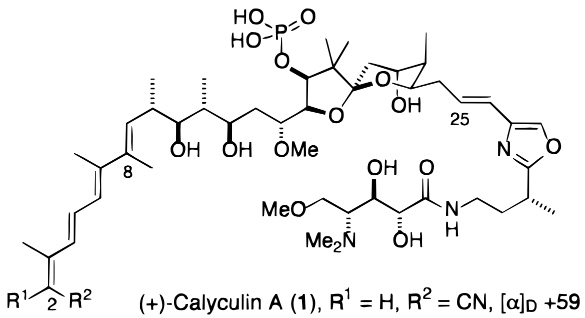
ABSTRACT



(+)-Calyculin A (**1**), R^1 = H, R^2 = CN, $[\alpha]_D$ +59
(−)-Calyculin B (**2**), R^1 = CN, R^2 = H, $[\alpha]_D$ -14

Calyculins A and B differ only by the (*E*)- vs (*Z*)-configuration at C(2). Yet, they show a large difference in optical rotations. We demonstrate a new strategy that provides a physical analysis of this long-range chiro-optical effect by Boltzmann-averaged atomic contribution mapping. The polarizability characteristics of the CN substituent rather than the perturbation of the stereogenic centers or the introduction of dissymmetry into the polyene chain give rise to the remarkable difference in rotation angles.

Calyculin A, an architecturally complex marine natural product, is used widely in the biological community as a standard for the evaluation of serine/theonine protein phosphatase inhibitors[1] and, not surprisingly, has attracted considerable interest in the synthetic community, culminating with several total syntheses.[2] During the recent total synthesis of calyculins A and B by Smith and co-workers,[2a] a fascinating stereochemical aspect of these molecules emerged. Surprisingly, calyculins A and B, which differ only by the (*E*)- vs (*Z*)-configuration at the terminal double bond in the tetraene subunit, demonstrate large differences in optical rotation: The (*Z*)-isomer **1** (*ent*-calyculin A) has an $[\alpha]_D$ of +59, whereas the (*E*)-isomer **2** (*ent*-calyculin B) has an $[\alpha]_D$ of −14.[3] It is truly remarkable that a change in the substitution at an alkene moiety separated by nine carbon atoms from the nearest asymmetric center induces a 70 unit

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(3) Natural calyculins A and B have $[\alpha]_D$ −60 and $[\alpha]_D$ +15, respectively. We thank Professors Nobuhiro Fusetani and Shigeki Matsunaga for confirming the optical rotation of natural calyculin B, which was previously reported as $[\alpha]_D$ −60.

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change in the specific rotation of a molecule with 15 constant stereocenters.

Although the conceptual framework for optical rotation has been known for some time,[4] the first reliable computations of optical rotation angles of organic molecules and complex natural products have appeared only in the last 2 years.[5] Optical rotation angles for many organic molecules have now been computed and shown to be accurate in both sign and magnitude.[5] However, simply computing optical rotations does not lead to structure−function relations that readily explain the paradox of the dramatic substituent effect on optical activity observed in the calyculins.

We have recently devised a quantitative method to dissect the trace of the electric dipole-magnetic dipole tensor (which is proportional to the rotation angle) into its atomic contributions.[5e] Atomic and group partitioning provides a foundation for establishing relationships among chemical structure and optical rotation angles. Here, we use $[\alpha]_D$ computations on models for calyculin A and B in order to understand the chemical origin of the unusual substituent effect. The changes observed in both the sign and magnitude of the specific rotation associated with the (*Z*)- vs (*E*)-isomerization remote from the stereogenic center might arise from the following: (1) differential cork-screw twisting of the π-system in the two structures; (2) differential changes in the electron distribution of the stereogenic center induced by through-bond interactions involving the remote cyanide; (3) electron polarizability effects localized at the cyanide substituent.

To address these competing effects, we built theoretical models for calyculin A and B based on truncated structures that include just two stereocenters and the terminal tetraene, as shown in Figure 1. We computed the electric-dipole magnetic-dipole polarizability tensor, G', and the optical rotation using coupled Hartree−Fock methods in the long-wavelength approximation for the model fragments **3** and **4**.[5a,b,e,g] G' is separated into atomic components, analogous to Mulliken population analysis, and the corresponding atomic contribution maps are used to address the structure−function issues posed earlier.[5e,g]

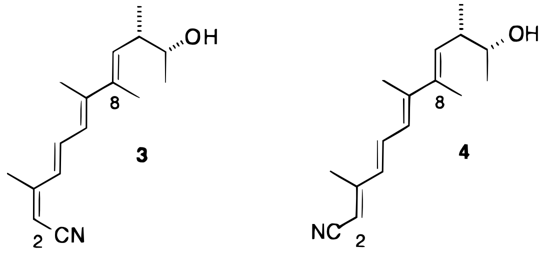

Figure 1. Calyculin fragments used in the computational analysis of the remote substituent effects in calyculins A and B.

The experimental measurements of specific rotation angles arise from a distribution of thermally accessible conformers in solution. Hence, our calculations of the specific rotational angles use conformations generated by a Monte Carlo search and are Boltzmann-weighted and summed to obtain the final computed specific rotation. We reported earlier that this conformational averaging is essential for reasonable agreement with experimental measures.[5a,e,g] For fragments **3** and **4**, we obtained 25 unique low energy conformations from Monte Carlo conformational searches with the Macromodel program using the MM2* force field and the chloroform continuum solvent model.[6] The specific rotations were computed using the CADPAC program with a Gaussian 6-31G basis set.[7] These rotations were Boltzmann-weighted and summed to obtain the specific rotation angle. All of the conformations that were within 6.5 kJ/mol of the lowest energy conformer were included in the Boltzmann sum. The

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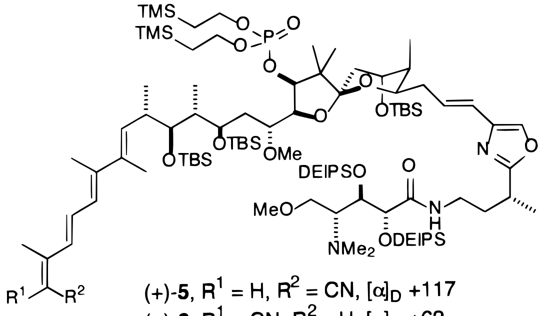
(7) The lowest energy conformers obtained by Monte Carlo sampling were minimized at every step and compared to see if the newly obtained structure was duplicated. If so, the duplicated structure was ignored. Only unique structures were retained. Low energy structures were usually chosen from a Monte Carlo sampling of 3000 conformations; each new conformation was minimized using a 3000-step energy minimization iteration method, forcing all the newly found structures to be fully relaxed. Taking the origin as the center of mass in the CADPAC calculations is expected to avoid substantive gauge origin dependent results for structures of this size (see ref 5g). Both in the X-ray and the MM2* (MacroModel) minimized structures as well as in ab initio calculations at the HF/6-31G**, DFT/B3LYP/6-31G*, MP2/6-31G, and MP2/6-31G* levels, the tetraene moiety is slightly bent, with only a few degrees of variation in the torsional angles between the different methods. For comparison, a complete listing of the computed ground state and the X-ray torsional angles can be found in the Supporting Information. Furthermore, while empirical force fields are poorly suited for the calculation of vibrational spectra of polyene chains (Schettino, V.; Gervasio, F. L.; Cardini, G.; Salvi, P. R. *J. Chem. Phys.* **1999**, *110*, 3241), conformational and torsional energies of conjugated compounds determined with MM2* (MacroModel) were found to provide excellent agreement with experimental values (Gundertofte, K.; Liljefors, T.; Norrby, P.-O.; Pettersson, I. *J. Comput. Chem.* **1996**, *17*, 429).

(8) Compounds (+)-**5** and (+)-**6** exhibited a difference of 55 $[\alpha]_D$ units (see Supporting Information of ref 2a). DEIPS = diethylisopropylsilyl, TBS = *tert*-butyldimethylsilyl, TMS = trimethylsilyl.



(+)-**5**, R^1 = H, R^2 = CN, $[\alpha]_D$ +117
(+)-**6**, R^1 = CN, R^2 = H, $[\alpha]_D$ +62

(9) For details of this methodology, see: Kondru, R. K.; Wipf, P.; Beratan, D. N., manuscript in preparation.

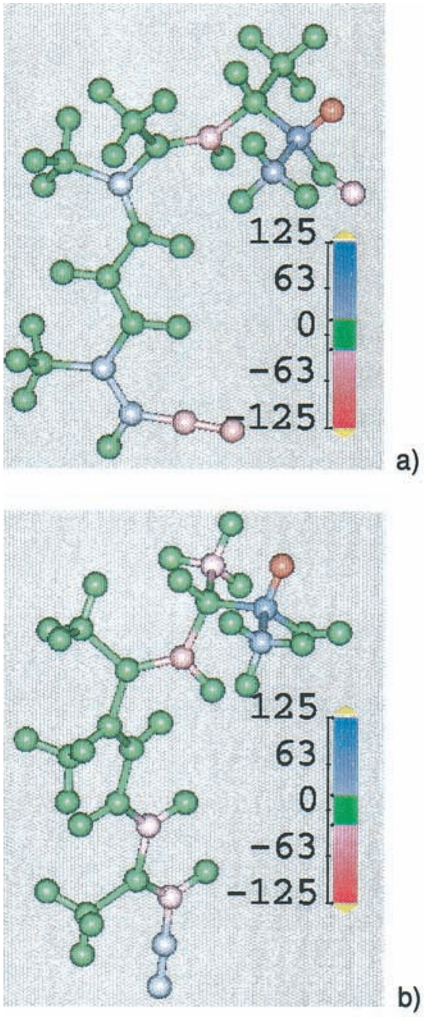


Figure 2. Boltzmann-averaged atomic contributions (BWAMs) to the specific rotation for (a) fragment **3**, the (*Z*)-configuration model for calyculin A, and (b) fragment **4**, the (*E*)-configuration model for calyculin B (see Figure 1 for molecular structures). The atoms are colored according to their contribution to the specific rotation angle. Atoms in green carry little contribution, red atoms have negative contributions, and blue atoms have positive contributions to the specific rotation angle. These maps highlight the large contribution arising from the CN substituent and the two adjacent carbon atoms.

Boltzmann-averaged rotation for fragments **3** and **4** was −46.1 and −88.1, respectively. Accordingly, the difference of 42 $[\alpha]_D$ units between (*Z*)- and (*E*)-configured calyculin models is only slightly less dramatic than that for the parent systems. Significantly, the trend for the (*E*)-configured tetraene to have a more negative $[\alpha]_D$ value is also reproduced in the model compounds **3** and **4** as well as in protected calyculins prepared during synthetic studies.[8]

Our atomic contribution maps reported earlier[5e,g] are readily interpreted for single conformations, but in a conformationally flexible molecule, a family of such maps must be Boltzmann-weighted to arrive at structure−function relations. As such, we have generated Boltzmann-weighted atomic maps (BWAMs) which take into account the thermally averaged contributions, displaying the data as a color-coded map on a single reference molecular structure.[9] BWAMs provide the first comprehensive approach to understanding how conformational averaging influences atomic/group contributions to the rotation angle. For example, averaging of this kind gives rise to van't Hoff's additivity principle of optical rotations. BWAMs for compounds **3** and **4** are shown in Figure 2. Both fragments show large contributions near the stereogenic centers. However, these local chiral perturbations are insensitive to the (*E*)- or (*Z*)-configuration of the terminal CN group. A decreasing atomic contribution to the rotation angle with distance from the chiral centers is observed. In contrast, the 2-cyano substituent and the adjacent carbon atoms make a substantial contribution that is at the source of the $[\alpha]_D$ shifts for **3** and **4**. This is readily illustrated by the *difference* BWAM, which is obtained by subtracting Figure 2b from 2a, shown in Figure 3.

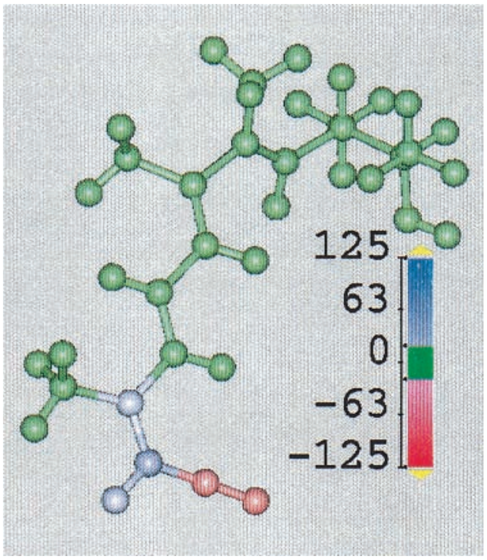


Figure 3. Shown is a *difference* BWAM map for fragments **3** and **4** where the atomic contributions for corresponding atoms in the (*Z*)- and (*E*)-configurations have been subtracted. For convenience, the values are displayed on the (*Z*)-isomer. The difference map clearly visualizes the dominance of the nitrile substituent over the optical activity. This difference map indicates that the influence of the alkene configuration on the optical rotation is *local*. For example, the effect does not arise from a long-range perturbation of the stereogenic carbons via the tetraene linkage.

In the coupled Hartree−Fock approach, contributions to the optical rotation are assigned to each occupied molecular orbital and—additionally—to each atomic orbital component of the molecular orbitals. Atomic maps take into account contributions to the optical rotation that arise from all occupied molecular orbitals. As such, it is possible for a symmetric region of the molecule to "light up" in a difference BWAM. Figure 3 shows that the difference in rotation angle in **3** and **4** arises from the cyano substituent and its two neighboring carbon atoms. Examination of this difference map allows us to reject the first and second hypotheses concerning the origin of the rotation differences in calyculins. Substantial changes are not induced in the stereogenic centers. Neither are substantial contributions to the rotation induced by cork-screwing of the tetraene. The difference BWAM shows that the effect is localized at the terminus of the tetraene and specifically due to the cyano substituent.

In conclusion, we have pinpointed the source of the large differences in the specific rotations for the (*Z*)-isomer **1** (*ent*-calyculin A) and the (*E*)-isomer **2** (*ent*-calyculin B) by analyzing structural models and carrying out specific rotation computations. The chiroptical analysis is assisted by constructing novel Boltzmann-weighted atomic contribution maps. We conclude that the differences in $[\alpha]_D$ between (*Z*)-**1** and (*E*)-**2** arise from the polarizability of the terminal cyanide substituent itself, rather than by a direct perturbation of the asymmetric centers in the (*Z*)- vs (*E*)-derivatives. The $[\alpha]_D$ effect is also not due to a dissymmetric twisting of the intervening unsaturated bridge. The electronic characteristics of the polarizable CN group and its effect on the immediate neighboring carbon−carbon bond control the difference in optical rotation in these structures. Most qualitative models for optical rotation emphasize the role played by both the polarizability and the transition dipole moments (through both their magnitude and orientation) of groups appended to the stereogenic centers.[10] Changing the CN position influences these fragment characteristics. The influence on optical rotation may be particularly strong because the extended π-electron pathway facilitates electronic communication between the CN group and the stereocenter, and the π-electron chain enhances the polarizability and transition moments that would otherwise be associated with an isolated CN group.[11] The mechanistic aspects of this electronic coupling are the subject of further investigation. We anticipate that other polarizable groups with accessible cis/trans derivatives such as enones and enoates coupled via conjugated π-electron pathways to stereogenic centers will display similar behavior and that the effect will depend on the dipole moment of the substituent as well as the strength of its coupling pathways with the stereogenic center. We are therefore actively pursuing optical rotation studies in other structures of this class.

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Supporting Information Available: Minimized (MM2* (MacroModel), HF/6-31G**, DFT/B3LYP/6-31G*, MP2/6-31G, MP2/6-31G*) and X-ray structure dihedral angles for calyculin fragment **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[11] We hypothesize that the tetraene unit serves as a topological coupler for the transition dipole moment interaction. Related effects of polyunsaturated chains have been observed, for example, for electron spin coupling (Tomioka, H.; Hattori, M.; Hirai, K.; Sato, K.; Shiomi, D.; Takui, T.; Itoh, K. *J. Am. Chem. Soc.* **1998**, *120*, 1106) and radiationless electronic energy transfer (Jensen, K. K.; van Berlekom, S. B.; Kajanus, J.; Mårtensson, J.; Albinsson, B. *J. Phys. Chem. A* **1997**, *101*, 2218).