



Unusual formation and helicity induction in a *para*-amino-substituted trityl chromophore: a cautionary note

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ABSTRACT

O- and N-trityl derivatives $\text{Ph}_3\text{C}^*-X-R^*$ of chiral alcohols ($X = \text{O}$) and amines ($X = \text{NH}$) are known to produce strong and stereochemically predictable Cotton effects in the Electronic Circular Dichroism (ECD) spectra due to the preferred *M* or *P* helical conformation of the trityl group. With the use of ECD spectra in solution and crystal X-ray diffraction analysis, we demonstrate that in a chiral *p*-substituted trityl derivative $p-R^*\text{N}(\text{Me})-\text{C}_6\text{H}_4-\text{C}^*\text{Ph}_2\text{H}$, the stereochemical information is transmitted from a permanent stereogenic center R^* to the dynamic C^* stereogenic center of the trityl sensor via the *para* carbon atom, and not through the central carbon atom.

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1. Introduction

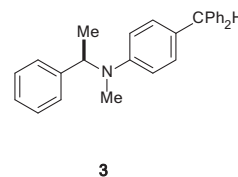
Tritylation of alcohols and amines with trityl chloride in the presence of a base is a well-established method of making O- or N-protected derivatives of alcohols or amines. These derivatives show the property of effective transmission of permanent chirality of the parent molecule to the dynamic helical structure of the trityl group. This was demonstrated by the induction of Electronic Circular Dichroism (ECD) due to the trityl chromophore which in such a case exists in a non-racemic equilibrium conformation ($[M] \neq [P]$) (Scheme 1).

We have demonstrated that the induced ECD spectra of the trityl chromophore indicate a relationship with the absolute configuration of the R^* group.^{1,2}

2. Results and discussion

Over the course of our work, we have found that while primary amines, such as (*R*)- α -methylbenzylamine, $\text{PhCH}(\text{Me})\text{NH}_2$ **1a** undergo ready N-tritylation with trityl chloride in the presence of triethylamine (NEt_3) in dichloromethane as a solvent at room temperature to give **2a**, the corresponding N-methyl derivative **1b** is much less reactive. No reaction was observed at room temperature in dichloromethane, tetrahydrofuran or pyridine as the

solvent, in the presence of NEt_3 . However at reflux temperature in THF or pyridine, with NEt_3 as a base, a reaction was observed and a tritylated product was isolated (20% yield), to which the structure **2b** was originally assigned on the basis of its ECD spectrum which was similar to the ECD spectrum of **2a**² (Scheme 2). However, a closer inspection of the ^1H NMR spectrum of the trityl derivative **1b** showed that in the aromatic region of the spectrum where the trityl group usually gives a complex multiplet signal at around $\delta = 7.2$, two doublets at δ 6.97 and 6.75, $J = 8.5$ Hz were observed. These signals could be ascribed to the presence of a *p*-substituted phenyl group in the trityl (Tr) moiety.^{3,4} Thus, instead of **2b**, the product of tritylation had structure **3** and this structure was confirmed by X-ray crystallography.⁵

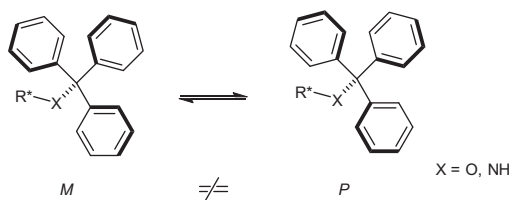


Structure **3** indicates that the reaction of secondary amine **1b** occurred from an attack of the nitrogen nucleophile at the electrophilic *para* position of the trityl group, rather than at the central carbon atom of the trityl group. On the other hand, tritylation of a similar but less congested secondary amine, N-methylbenzylamine at room temperature with trityl chloride and NEt_3 gave the

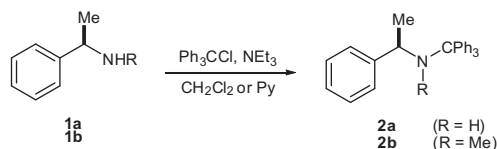
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Scheme 1. Conformational equilibrium of chiral trityl ethers and amines.



Scheme 2. N-Trityl derivatization of benzylamines.

expected *N*-methyl-*N*-tritylbenzylamine. The same course of reaction was observed with benzylamine **4**. It is known that the reaction of trityl electrophile with phenols and anilines occurs at the *para*-position of the activated aromatic ring, with the formation of a carbon–carbon bond.⁶ Clearly, the course of alkylation of aliphatic amines with trityl chloride is dependent on the reaction conditions and steric demands, which are at their greatest in the case of **1b**.

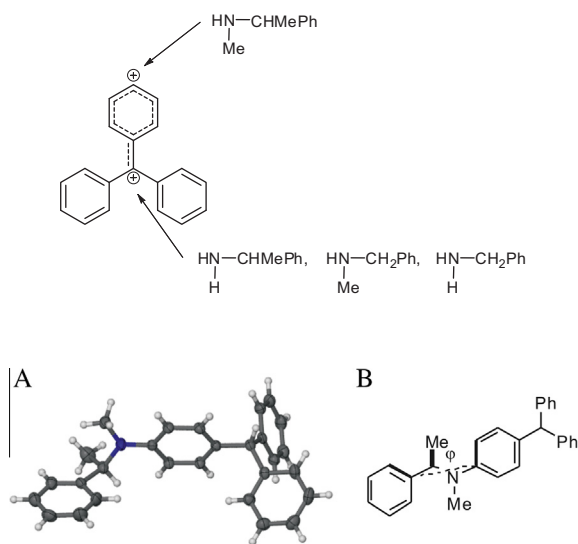


Figure 1. Crystal structure of **3** (A) and definition of dihedral angle φ (B). Of the four possible values of angle φ , the smallest absolute value is always chosen. For a 3D structure see [Supplementary information](#).

Single crystal X-ray analysis of the reaction product, obtained by crystallization from ethyl acetate, confirmed that the product was indeed **3**. The structure of **3** is shown in [Figure 1](#).

The characteristic structural features of **3** are the (*R*)-configuration of its stereogenic carbon atom, the coplanarity of the three N–C bonds, i.e., N–Me, N–Tr and N–C_{chiral} (*sp*² hybridized nitrogen atom) and the planarity of each aromatic ring. The conformational flexibility of the molecule is due to the changes of dihedral angle φ ([Fig. 1](#)) and due to the presence of rotamers of the phenyl groups in the trityl moiety, described by a set of three angles ω , defined in Ref. [1](#). In the crystal structure, the values of ω are -38° , -50° and -55° (*MMM* type of helicity) whereas angle φ is -61° .

In order to gain a more complete picture of the low energy conformers of **3**, we performed a conformational search at the DFT level, using 6-311++g(d,p) functional and B3LYP basis set. Among the seven conformers calculated within the relative energy window 0 to 2.94 kcal mol⁻¹, only five conformers that have population above one percent were taken into consideration. In this group only two types were found, with respect to the helicity of the trityl group. The structures of the trityl groups in these conformers are close to C₃ symmetry, either *PPP* or *MMM* ([Fig. 2](#)) and numerical values of pseudo-torsion angles $|\omega|$ are relatively similar, in the range of 50–58 degrees ([Table 1](#)).

Table 1

Calculated energies, populations and pseudotorsion angles ω and φ for the low energy conformers of **3.1–3.5**

	ΔG [kcal mol ⁻¹]	Population [%]	ω [°]	φ [°]
3.1	0.00	55.5	–50, –53, –55	–72
3.2	0.29	33.7	54, 54, 54	–73
3.3	1.50	4.2	51, 54, 56	–17
3.4	1.76	2.7	–52, –52, –54	–18
3.5	1.78	2.6	53, 54, 55	35

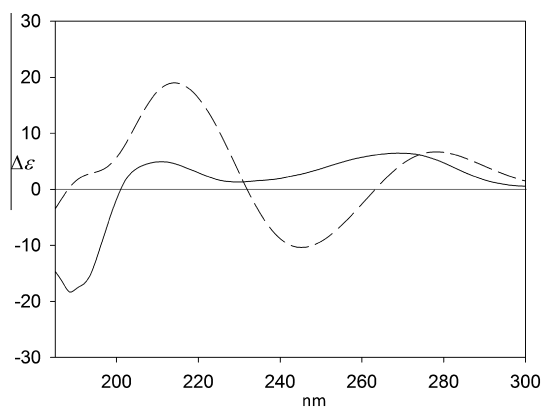


Figure 3. ECD spectra of **3**: measured in acetonitrile solution (—) and calculated (---), see text.

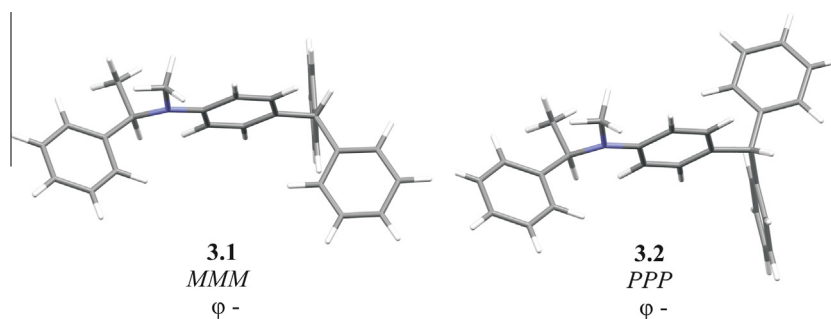


Figure 2. The calculated two lowest energy conformers **3.1** and **3.2**.

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