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Unusual formation and helicity induction in a para-aminosubstituted trityl chromophore: a cautionary note

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ABSTRACT

O- and N-trityl derivatives $Ph_3C^*-X-R^*$ of chiral alcohols (X = O) and amines (X = 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 $p-R^*N(Me)-C_6H_4-C^*Ph_2H$, 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, PhCH(Me)NH₂ **1a** undergo ready N-tritylation with trityl chloride in the presence of triethylamine (NEt₃) 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 NEt₃. However at reflux temperature in THF or pyridine, with NEt₃ 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 δ = 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 psubstituted 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 NEt₃ 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} (sp² 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 C_3 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.



Figure 4. Calculated structure of the lowest energy conformer of 2a and experimental ECD spectrum of 2a in acetonitrile.

In conformers 3.1–3.5 the trityl group forms a propeller, attached to the rest of the molecule by an axis formed by the C_{para} -N bond. Statistically, the P-type propeller conformers are slightly less populated (41%) compared to their M-type counterparts (58%). This is because the trityl central carbon atom is separated by six bonds from the molecule's stereogenic center and there is weak stereodifferentiating steric crowding around the trityl group. The differences between conformers of **3**, involving angle φ , are more significant. The absolute values of φ are between 17° and 73° and conformers with $\varphi < 0$ dominate (96%) over conformers having $\phi > 0$ (3%). Negative values of ϕ in conformers **3.1** and **3.4** are associated with the negative values of angles ω . These conformers (negative values of ω and φ , population 58%) strongly dominate over their diastereoisomers with positive values of both ω and φ angles (3%). Moreover, the structure of the conformer present in the crystal matches very well with the structure of the lowest energy conformer **3.1** [compare Figs. 1A and 2(**3.1**)]. ECD spectra were simulated for the five lowest energy conformers 3.1-3.5 and the final spectrum presented in Figure 3 is an average of all simulated spectra with population weighting.

For comparison, the structure of trityl derivative 2a is typical for tritylated chiral amines. According to calculations, the dominating conformer (92% population), shown in Figure 4, has a more compact structure, the environment of the nitrogen atom is tetrahedral [(S)-configuration] and the trityl group displays only very approximate C_3 symmetry of *PPP* helicity (angles ω are 19, 27, 77°). Other conformers of 2a are of MMP (6%) and MMM (2%) helicity. These conformers are much less populated and do not significantly contribute to the ECD spectrum of 2a.

3. Conclusion

In conclusion, we have determined the structure of the tritylation product of *N*-methyl- α -methylbenzylamine. In this product the trityl group is N-substituted at the para rather than at the central position, a situation not previously encountered in the reaction of trityl chloride with aliphatic amines. Despite its extended structure, the trityl derivative **3** shows a significantly strong ECD spectrum in the region of trityl chromophore absorption spectrum. Although the trityl group in 3 is dynamically nearly racemized, this compound displays strong Cotton effects because of phenyl/p-phenylene groups electronic excited state interaction in conformationally biased structure. Such a situation is intuitively not obvious and the result is a caution against the use of empirical models for CD spectra interpretation, not based on a detailed computational analysis.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetasy.2016.07.011.

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- Experimental data for **3**: mp 99–102 °C; $[\alpha]_D^{23} = +180$ (*c* 0.15, CH₂Cl₂); ¹H NMR (CDCl₃): $\delta = 7.23$ (m, 15H), 6.97 (d, *J* = 8.5 Hz, 2H), 6.75 (d, *J* = 8.8 Hz, 2H), 5.46 (s, 3 1H), 5.08 (q, J = 6.9 Hz, 1H), 2.65 (s, 3H), 1.52 (d, J = 6.9 Hz, 3H); ³C NMR $(CDCl_3)$: $\delta = 148.53$, 144.67, 142.89, 131.84, 130.05, 129.38, 128.31, 128.14, 126.87, 126.75, 125.99, 112.76, 56.51, 55.92, 31.82, 16.28.



- **4.** The minor product found in low concentration in the crude reaction mixture by the GC–MS analysis was presumably *p*-Ph₂HC-C₆H₄-CPh₃ (*m*/*z* = 486) as reported by Huszthy, P.; Lempert, K. J. Chem. Soc., Perkin Trans. 2 **1985**, 1323–1329.
- 5. Crystal data for **3:** $C_{28}H_{27}N$, $M_r = 377.50$, colourless plate, 0.24 × 0.20 × 0.08 mm³, monoclinic, space group $P2_1$ (No. 4), a = 9.3250(2), b = 8.6664(1), c = 13.7611(2)Å, $\beta = 102.182(2)^\circ$, V = 1087.05(3)Å³, Z = 2, $D_c = 1.153$ g/cm³, F000 = 404, SuperNova, Atlas detector, CuK α radiation, $\lambda = 1.54178$ Å, T = 294.0(1) K, $2\theta_{max} = 151.7^\circ$, 9532 reflections collected, 4164 unique ($R_{int} = 0.0106$). Final GooF = 1.034, R1 = 0.0303, wR2 = 0.0855, R indices based on 4043 reflections with I > 2 sigma(I) (refinement on F^2), 317 parameters, 97 restraints. Lp and absorption corrections applied, $\mu = 0.498$ mm⁻¹. Absolute structure parameter = 0.0(3).

The structure was solved by direct methods using SHELXS97 and refined by the full-matrix least-squares techniques with SHELXL97. All heavy atoms were refined anisotropically. The hydrogen atoms bound to C atoms were placed at calculated positions and refined using a riding model, and their isotropic displacement parameters were given a value 20% higher than the isotropic

equivalent for the atom to which the H atoms were attached (for methyl hydrogens this value has been increased to 50%).

In the crystal, the phenyl ring directly attached to stereogenic centre was found to be disordered over two positions and refined with fixed occupancies of 0.65 and 0.35. The ADP restraint (SIMU) and rigid-bond restraint (DELU) for disordered part of molecule were applied. This, presumably dynamic disorder of the phenyl substituent did not affect mutual orientation of the two phenyl chromophores discussed in the paper, i.e., the amine and the *para* substituted phenyl groups.

CCDC-1491957 contains the supplementary crystallographic data for this paper. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data%5Frequest/cif.

6. For example, *p*-aminotetraphenylmethane can be obtained by the reaction of aniline with trityl chloride, see MacKenzie, C. A.; Chuchani, G. J. Org. Chem. 1955, 20, 336–345. or by the reaction of triphenylmethanol with aniline hydrochloride, see; Witten, B.; Emmet Reid, E. Org. Synth. Coll. 1963, Vol. IV, 47–48.