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Optical Rotation Measurements of Organometallic Compounds: Caveats and Recommended Procedures

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Summary: There are many possible sources of error in determining specific rotations, $[\alpha]^T_\lambda$, of chiral, nonracemic organometallic compounds (e.g., purity, sample mass, solution volume, temperature). These are systematically analyzed, and recommended procedures are outlined. Protocols for calculating 95% confidence limits are given.

The first optically active transition metal complexes were reported in 1911.[1] However, during the last decade there has been dramatically increasing interest in chiral, nonracemic organometallic complexes.[2] This derives from a variety of exciting new applications in mechanistic studies, Ziegler–Natta catalysis, and enantioselective syntheses.

Consequently, many new optically active organometallic complexes are being synthesized and characterized by their specific rotations, $[\alpha]^T_\lambda$. Although polarimetry is one of the oldest instrumental techniques in chemistry,[3] is is not a familiar one for most inorganic and organometallic chemists. Further, none of the modern methods for determining enantiomeric excesses (ee)—such as chiral NMR shift reagents and chromatography[4–7]—have rendered (to the regret of many)[8] polarimetry obsolete. Hence, in this note we compile some caveats and recommendations based upon our extensive experience with optically active chiral organorhenium complexes.[9] We believe these will aid researchers who are new to this field.

1. Purity of Compounds. For many chiral molecules, enantiomerically pure samples do not crystallize as readily as racemic samples.[10] Thus, the former can be much more difficult to purify. *A procedure that gives a racemic compound in analytically pure form is by no means guaranteed to give the corresponding enantiomerically pure compound in analytically pure form.* Hence, microanalyses (and other solid state properties such as melting points) should be redetermined. Any impurity, or subsequently generated thermal decomposition or oxidation product, can greatly affect the observed rotation α.

To illustrate the potential effect of a small amount of sample oxidation, we added 1 mol % of the radical cation $[(\eta^5\text{-}C_5H_5)_2Fe]^{\bullet+}PF_6^-$ to a CH_2Cl_2 solution of the methyl complex $(+)\text{-}(S)\text{-}(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)(CH_3)$, with $[\alpha]_{589}^{25} = 180 \pm 4°$ (≥99% ee).[9] This compound normally exhibits excellent configurational stability. However, over the course of 1 h under an inert atmosphere, $[\alpha]_{589}^{25}$ dropped to 29 ± 5°! Brunner has reported similar phenomena with optically active, diastereomeric cyclopentadienyliron complexes.[11]

Hence, if it proves necessary to determine $[\alpha]^T_\lambda$ for a sample that is not analytically pure (a situation we have occasionally found unavoidable),[12] it should be explicitly stated. Extra handling precautions should be taken with thermally or oxidatively sensitive materials.

2. Minimization of Weighing Errors. By some criteria, concentrated samples are desirable in spectroscopy. Errors in weighing and the measurement of weak absorbances can be minimized. However, many organometallic compounds strongly absorb visible light. If insufficient light is transmitted through the polarimeter cell, especially at the 589-nm wavelength most commonly utilized, readings become impossible. Thus, the specific rotations of many chiral organometallic compounds are of necessity determined on dilute solutions—often such that the amount of substrate in the cell is less than 1 mg.

A related consideration is that most enantiomerically pure organometallic compounds give $[\alpha]^T_\lambda$ values of >100°. Hence, it is important to follow a protocol that ensures a minimum of three significant digits. All of these concerns can be addressed as follows. First, weight out *at least* a 0.0100-g sample. On standard analytical balances, this quantity can be assigned a 95% confidence limit, Δ(weight) or $\Delta(w)$,[13] of ±0.0002 g.[14] Next, prepare a standard solution in a volumetric flask, for which 95% confidence limits, Δ(volume) or $\Delta(v)$,[13] have been determined.[15] for 10-, 25-, and 50-mL volumetric flasks, values are ±0.02, ±0.03, and ±0.05 mL, respectively.[15] These quantities will be propagated through to 95% confidence limits for $[\alpha]^T_\lambda$ values as described below.

3. Temperature Control. The volume of a solution is temperature dependent and, consequently, so is the concentration of any solute. An example worked in a text[13] shows that the change in density of water between 18 and

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[11] Brunner, H.; Fisch, K.; Jones, P. G.; Salbeck, J. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1521.

[12] Agbossou, F.; Ramsden, J. A.; Huang, Y.-H.; Arif, A. M.; Gladysz, J. A. *Organometallics* **1992**, *11*, 693.

[13] Abbreviations follow the standard in: Shoemaker, D. P.; Garland, C. W. *Experiments in Physical Chemistry*, 5th ed.; McGraw-Hill: New York, 1989; p 55. The symbol $\Delta(x)$ designates a 95% confidence interval and signifies that x [illegible] $\Delta(x)$ has a 95% probability of containing the true value of the quantity x. This book also utilizes polarimetry as the basis for an amusing anecdote regarding error analysis. The treatment presented in this paper was developed independently.

[14] This value is calculated from the repeated weighing of a standard sample on our analytical balance and corresponds to two standard deviations (2σ).

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25 °C should only affect α by a factor of 0.998625/0.997075, or <0.02%. This is small compared with other sources of error. However, the densities or common organic solvents such as ethanol or CH_2Cl_2 can change by 1–2% between 15 and 25 °C.[16]

Of potentially greater impact are the diverse types of temperature-dependent equilibria that can be encountered with organometallic compounds. For example, the benzaldehyde complex (+)-(*RS*)-$[(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)(O{=}CHC_6H_5)]^+BF_4^-$ exists as a mixture of π (major) and σ (minor) linkage isomers.[17] The ratios are strongly temperature and solvent dependent. Thus, if the limiting structures have appreciably different specific rotations, $[\alpha]^T_\lambda$ should be a sensitive function of temperature and solvent. Data acquired in CH_2Cl_2 (uncorrected for the change in CH_2Cl_2 density with temperature) are as follows: $[\alpha]_{589}{}^{30.8} = 317°$, $[\alpha]_{589}{}^{26.1} = 306°$, $[\alpha]_{589}{}^{14.5} = 280°$, $[\alpha]_{589}{}^{0.9} = 269°$, $[\alpha]_{589}{}^{-11} = 254°$.[17a]

Most polarimeter cells are jacketed. Hence, they should be attached to a commercial circulating water bath for precise temperature control.

4. Polarimeter Readings. We advise that at least 15–30 readings of α be taken. These are in turn utilized to calculate the average (mean) and the standard deviation (σ) of α. This can be done on any scientific calculator, common statistics programs such as Statview,[18a] or spreadsheets such as Microsoft Excel.[18b] The standard error of the mean, SEM,[19] and the 95% confidence limit in the mean, $\Delta(\alpha)$,[13] are given by eq i and ii. In these formulas, N is the number of readings taken, and $t_{0.95}$ is a commonly utilized statistical function that depends upon N.[20]

$$\mathrm{SEM} = \sigma(N^{-1/2}) \qquad \text{(i)}$$

$$\Delta(\alpha) = t_{0.95}(\mathrm{SEM}) \qquad \text{(ii)}$$

The derivation and interpretation of $t_{0.95}$ values are discussed at length in a variety of sources.[20] The program Statview can do a complete calculation from raw data. The $\Delta(\alpha)$ values are applied as described below.

5. Calculation of $[\alpha]^T_\lambda$ and $\Delta([\alpha]^T_\lambda)$. The specific rotation $[\alpha]^T_\lambda$ is calculated from eq iii. We will first comment upon several potential points of confusion regarding the application of this well-known formula.

$$[\alpha]^T_\lambda = \alpha/lc \qquad \text{(iii)}$$

In the convention adopted by most reference texts,[21] c is the concentration in g/mL and l is the path length in *decimeters*. However, in other books the alternative shown in eq iii′ can be found.[22] Here, concentration (c') is given

$$[\alpha]^T_\lambda = 100\alpha/lc' \qquad \text{(iii}'\text{)}$$

in units of g/100 mL. A factor of 100 is added to the numerator to yield the same $[\alpha]^T_\lambda$ value as eq iii. As a result of this dual formalism, *different researchers utilize different units of c*. This lack of an absolute standard complicates concentration specifications, as considered below. Other variations of eq iii have also appeared in the literature.[23]

We find it instructive to consider the following equivalent definition of $[\alpha]^T_\lambda$: the amount of rotation (deg) by a 1.00-g sample in 1.00 mL of solvent in a tube of length 1.00 dm at a specified temperature and wavelength. This syntax emphasizes that $[\alpha]^T_\lambda$ has units of (deg·mL)/(g·dm). Unfortunately, these have been historically ignored. If units were routinely designated, researchers would be less dependent upon a "blackbox" formula for calculating $[\alpha]^T_\lambda$.

Despite any shortcomings, eq iii easily lends itself to a propagated error analysis.[24] This gives iv, where the Δ^2 terms in the numerators are squares of the 95% confidence limits, and experimental quantities are in the denominators.

$$\frac{\Delta^2([\alpha]^T_\lambda)}{([\alpha]^T_\lambda)^2} = \frac{\Delta^2(\alpha)}{(\alpha)^2} + \frac{\Delta^2(c)}{(c)^2} + \frac{\Delta^2(l)}{(l)^2} \qquad \text{(iv)}$$

We first simplify eq iv by eliminating the final term, which propagates the error in path length l. The 1-dm cell that accompanies the polarimeter utilized for this study (Perkin-Elmer Model 241 MC) is calibrated by the manufacturer to five significant digits (100.01 mm). Therefore, any systematic error in the path length will affect α by less than 0.1%. Next, the concentration term in eq iv can be expressed in terms of sample weight and volume, as shown in eq v.

$$\frac{\Delta^2(c)}{(c)^2} = \frac{\Delta^2(w)}{(w)^2} + \frac{\Delta^2(v)}{(v)^2} \qquad \text{(v)}$$

Substitution of eq v into eq iv yields eq vi.

$$\frac{\Delta^2([\alpha]^T_\lambda)}{([\alpha]^T_\lambda)^2} = \frac{\Delta^2(\alpha)}{(\alpha)^2} + \frac{\Delta^2(w)}{(w)^2} + \frac{\Delta^2(v)}{(v)^2} \qquad \text{(vi)}$$

Equation vi is then solved for $\Delta([\alpha]^T_\lambda)$, the 95% confidence limit of $[\alpha]^T_\lambda$, utilizing the quantities specified above. To summarize, α is the average of the observed rotations read from the polarimeter, $\Delta(\alpha)$ is the 95% confidence limit determined from eq ii, w is the sample

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(15) (a) Peffer, E. L.; Mulligan, G. C. *Testing of Glass Volumetric Apparatus*; U.S. National Bureau of Standards Circular 602; U.S. Government Printing Office: Washington, DC, 1959. Abstracted in ref 13, p 770. (b) Rigorously, a volumetric flask must be used at the calibration temperature (usually 20 °C) or a correction of 0.0025%/°C added or subtracted to the volume (*CRC Handbook of Chemistry and Physics*, 71st ed.; Lide, D. R., Ed.; CRC: Boca Raton, FL, 1990; pp 15–17). However, in the normal room temperature range of 19–23 °C the error introduced by neglecting this correction (±0.01%) is insigificant compared to the other sources of error analyzed below.

(16) Extensive tabulations of densities as a function of temperature are given in: *Industrial Solvents Handbook*, 4th ed.; Flick, E. W., Ed.; Noyes Data Corp.: Park Ridge, NJ, 1991. Selected data also appear in the *Merck Index*.

(17) (a) Garner, C. M.; Quirós Méndez, N.; Kowalczyk, J. J.; Fernández, J. M.; Emerson, K.; Larsen, R. D.; Gladysz, J. A. *J. Am. Chem. Soc.* **1990**, *112*, 5146. (b) Quirós Méndez, N.; Seyler, J. W.; Arif, A. M.; Gladysz, J. A. *Ibid.* **1993**, *115*, 2323.

(18) (a) Abacus Concepts, Inc., Berkeley, CA, 1992. (b) Microsoft Inc., Redmond, WA, 1992.

(19) (a) Freedman, D.; Pisani, R.; Purves, R. *Statistics*; W. W. Norton: New York, 1980; p 409. (b) Snedecor, G. W.; Cochran, W. G. *Statistical Methods*, 8th ed.; Iowa State University Press: Ames, 1989; p 53. (c) Reference 13, p 44.

(20) The $t_{0.95}$ values can also be obtained from tables (ref 19a, p A-71; ref 19b, p 466). For N of 15, 30, and ∞, $t_{0.95}$ is 2.15, 2.05, and 1.96. For further details see (a) ref 19a, p 409; (b) ref 19b, p 53; (c) ref 13, p 45.

(21) (a) March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley: New York, 1992; p 96. (b) Morrison, R. T.; Boyd, R. N. *Organic Chemistry*, 5th ed.; Allyn & Bacon: Boston, 1987; p 128.

(22) (a) Adamson, A. W. *A Textbook of Physical Chemistry*, 3rd ed.; Academic Press: New York, 1986; p 851. (b) Lyle, G. G.; Lyle, R. E. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 1, Chapter 2. (c) Reference 13, p 728.

(23) For example, ref 13, p 37: $[\alpha] = (V/ml)\alpha$ where V is the volume of the standard sample solution in mL, m is the mass of solute added in g, and α and l are as in eq iii. Note that V/m is equal to $1/c$.

(24) See ref 13, pp 57–58.

weight, $\Delta(w)$ is the weighing error (usually ±0.0002 g),[14] v is the volumetric flask size, and $\Delta(v)$ is from the NBS table (±0.02, ±0.03, and ±0.05 mL for 10-, 25-, and 50-mL flasks).[15]

With typical sets of α readings and weights and volumes in the ranges given above, it becomes apparent that the magnitude of the 95% confidence limit $\Delta([\alpha]^T_\lambda)$ is usually dominated by the weight term in eq vi. In some cases, the α term is larger. However, $\Delta(\alpha)$ can usually be optimized by a second determination utilizing a different sample concentration.

6. Miscellaneous Points. The following also deserve emphasis in our experience.

(A) Indicate the Concentration, with Units, and Solvent after $[\alpha]^T_\lambda$. Specific rotations are often reported as follows: $[\alpha]^T_\lambda$ **x°** ($c = z$; solvent). A standard of g/100 mL is loosely recognized for c. However, the situation is confused by contrasting definitions of $[\alpha]^T_\lambda$, which can utilize different units of c, as illustrated in eq iii and iii′ above. Thus, we recommend that units always be specified with c to prevent ambiguity. When enantiomeric excesses are to be calculated from $[\alpha]^T_\lambda$ values, the concentration of the unknown sample should be close to that of the reference or literature sample. However, $[\alpha]^T_\lambda$ is usually strongly concentration dependent only in special cases where equilibrium with a dimer or other type of aggregated species can occur.[22b]

(B) Watch for Mutarotation. A sample may crystallize as one of two isomers. However, equilibration to a mixture of isomers may occur over a period of time. Hence, a reading taken 10 min after a sample has been dissolved may differ from that taken after 10 h. Such behavior is commonly observed with alkylidene complexes $[(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)({=}CHR)]^+X^-$, which crystallize as one Re═C geometric isomer but slowly equilibrate to ca. 90:10 mixtures of isomers in solution at room temperature.[25]

(C) Different Salts of Optically Active Cations Give Different $[\alpha]^T_\lambda$. Consider a salt $R^{*+}X^-$ in which only the cation (or anion) is chiral. The observed rotation α is divided by the *weight* concentration (g/mL) as opposed to the molar concentration (e.g., mmol/mL) to give $[\alpha]^T_\lambda$. For ideal solutions that obey Beer's law, α will depend only upon the concentration of the cation in the path length. Consider next the tetrafluoroborate and hexafluorophosphate salts $R^{*+}BF_4^-$ and $R^{*+}PF_6^-$. Obviously, α will be equal when *solutions with equimolar concentrations* are utilized. However, $[\alpha]^T_\lambda$ is obtained by dividing α by g/mL, which is *not* the same for equimolar solutions of the two salts. If R^{*+} has a formula weight of 400, it can be calculated that $[\alpha]^T_\lambda$ for $R^{*+}BF_4^-$ will be 12% greater than that for $R^{*+}PF_6^-$.

7. A Worked Example. A sample of (+)-(*SR*)-$[(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)(NH_2CH(CH_3)Ph)]^+TfO^-$ (0.0292 ± 0.0002 g)[26a] was weighed directly into a 50-mL volumetric flask ($\Delta(v)$ = 0.05 mL), and CH_2Cl_2 was carefully added to the mark. A ca. 1-mL polarimeter cell (l = 1 dm) was first rinsed with and then charged with the resulting solution. The cell was attached to a circulating water bath thermostated at 25 °C. After an interval for temperature equilibration, 22 readings of α were taken over 30 min (0.235°, 0.236°, 0.225°, 0.226°, 0.233°, 0.233°, 0.234°, 0.229°, 0.229°, 0.234°, 0.231°, 0.235°, 0.233°, 0.230°, 0.231°, 0.235°, 0.230°, 0.236°, 0.234°, 0.228°, 0.235°, 0.234°; energy transmittance 55%). These gave α (average) = 0.232°, σ = 0.003°, SEM = 0.0007° (eq i), $t_{0.95}$ = 2.09,[20] and $\Delta(\alpha)$ = 0.00146° (eq ii). Quantities were then substituted into eq vi as follows:

$$\frac{\Delta^2([\alpha]_{589}{}^{25})}{(397°)^2} = \frac{(0.001\,46°)^2}{(0.232°)^2} + \frac{(0.0002\text{ g})^2}{(0.0292\text{ g})^2} + \frac{(0.05\text{ mL})^2}{(50\text{ mL})^2} \quad \text{(vii)}$$

$$\frac{\Delta^2([\alpha]_{589}{}^{25})}{(397°)^2} = 0.000\,04 + 0.000\,05 + 0.0000\,01 \quad \text{(viii)}$$

$$\Delta([\alpha]_{589}{}^{25}) = 4° \quad \text{(ix)}$$

Application of eq iii then gives $[\alpha]_{589}{}^{25} = 397 \pm 4°$ (c = 0.584 mg/mL, CH_2Cl_2).[26] Importantly, the 95% confidence limit of ±4° is due mainly to the weight term in eqs vii and viii (ca. 55%). Also, the 95% confidence limit is 1% of the specific rotation $[\alpha]_{589}{}^{25}$. Thus, any calculations of enantiomeric excesses based upon $[\alpha]_{589}{}^{25}$ are reliable only to ±1%, even in the absence of systematic errors. Also, a change of only 0.002° in α (average) would give nearly a 1% change in $[\alpha]_{589}{}^{25}$.

If the sample mass is doubled to 0.0584 g in the preceding example, the weight term in eq viii decreases to 0.000 01 and the 95% confidence limit improves to ±3°. However, optically active compounds are not always available in quantity, and this constitutes a much larger mass than is needed to completely characterize a new compound by NMR, IR, MS, and microanalysis. If α (average) is decreased by 50% in the preceding example, the α term in eq viii increases to 0.0002 and $[\alpha]_{589}{}^{25} = 199 \pm 3°$. Now the 95% confidence limit is >1% of $[\alpha]_{589}{}^{25}$. Hence, some of the limitations of optical rotation data are readily apparent from this worked example.

8. Summary. This note has pointed out some of the unique problems associated with determining specific rotations of organometallic and inorganic compounds. However, many of the issues analyzed are equally applicable to optically active compounds that lack metals. It is evident from the worked example, which is a representative case and not a "worst" case, why other methods of determining enantiomeric excesses are being actively developed and enthusiastically embraced.

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[26] For examples of $[\alpha]^T_\lambda$ with 95% confidence limits calculated by this procedure, see ref 17a and: (a) Dewey, M. A.; Gladysz, J. A. *Organometallics* **1990**, *9*, 1351. (b) Dalton, D. M.; Fernández, J. M.; Emerson, K.; Larsen, R. D.; Arif, A. M.; Gladysz, J. A. *J. Am. Chem. Soc.* **1990**, *112*, 9198. (c) Dewey, M. A.; Knight, D. A.; Klein, D. P.; Arif, A. M.; Gladysz, J. A. *Inorg. Chem.* **1991**, *30*, 4995. (d) Dewey, M. A.; Knight, D. A.; Arif, A. M.; Gladysz, J. A. *Z. Naturforsch., B: Anorg. Chem., Org. Chem.* **1992**, *47*, 1175.