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Substituent effect in theoretical VCD spectra

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The first systematic study on substituent effect in theoretical VCD spectral parameters is reported. The VCD spectra of 5-substitueted indenes revealed strong correlations of ν(C*H) and ν(CN) VCD intensities with σ_p or pEDA(I) descriptors. We also report correlations of VCD intensity factors as well as VCD sign-change with substituent.

Substituent effect continues to be a key concept in physical organic chemistry. Small changes in molecular structure upon introduction or exchange of a substituent are reflected in many properties important from the point of view of different branches of chemistry. It is therefore essential to describe the effect in a quantitative manner and to this aim several substituent effect scales were introduced. Most widely known are Hammett σ constants, which, not without modifications, were used to analyze different physical properties for a wide spectrum of chemical systems. This resulted in numerous excellent correlations in fields of chemical reactivity, kinetics, mass spectrometry, polarography, NMR and IR spectra parameters, and many others, offering chemists an important explanatory and predictive tool for their research.[1]

One of the most dynamically developing spectroscopy types is vibrational circular dichroism (VCD), which even though began to appear in 1970s, only quite recently started to be relatively routinely applied to problems of chiral chemistry (enantiomeric purity, absolute configuration determination, assymetric synthesis etc.). This is possible mainly thanks to instrumentation development and increase in computational power, allowing for quite inexpensive VCD spectra simulation.[2]

As to date, even not a single correlational analysis of VCD parameters was published, even though there were some rather qualitative analyses. In 1983 Nafie et al. compared methine stretching mode in VCD of several amino acids,[3] then in 1999 his extended group tackled hydrogen stretching in some methyl lactate derivatives.[4] In 2007 scientists from Wyeth Research considered differently substituted phenylglycidols.[5] We decided to apply

correlational analysis to the parameters of calculated VCD spectra. It is the first study on substituent effect in vibrational circular dichroism.

The model compounds chosen for the study were 5-substituted 1-cyano-1H-indene (CN-IND) and 1-isocyano-1H-indene (NC-IND), which can be considered as rigidified derivatives of a para-substituted benzene with attached chirality center (Scheme 1). The cyano and isocyano groups were introduced because of their well-isolated ν(CN) and ν(NC) stretching modes. We examined an exhaustive set of 28 substituents that covered evenly whole range of Hammett σ_p constants and pEDA(I) descriptors (Table 1).[6,7]

TABLE 1. Substituents used in the study along with their σ_p and pEDA(I) values.

| substituent	σ_p	pEDA(I) [e]	substituent	σ_p	pEDA(I) [e]
BF_2	0.48	-0.078	$MeSO_2$	0.72	-0.016
Br	0.23	0.057	NH_2	-0.66	0.141
CHO	0.42	-0.088	$NHNH_2$	-0.55	0.133
Cl	0.23	0.064	NMe_2	-0.83	0.177
$COCH_3$	0.50	-0.071	NO	0.91	-0.132
$CONH_2$	0.36	-0.044	NO_2	0.78	-0.069
$COOCH_3$	0.45	-0.062	OCF_3	0.35	0.040
COOH	0.45	-0.069	OH	-0.37	0.114
Et	-0.15	0.011	OMe	-0.27	0.120
F	0.06	0.068	SH	0.15	0.096
H	0.00	0.000	SiH_3	0.10	-0.012
iPr	-0.15	0.007	$SiMe_3$	-0.07	-0.011
Me	-0.17	0.016	tBu	-0.20	0.008
MeS	0.01	0.108	Vin	-0.04	-0.009
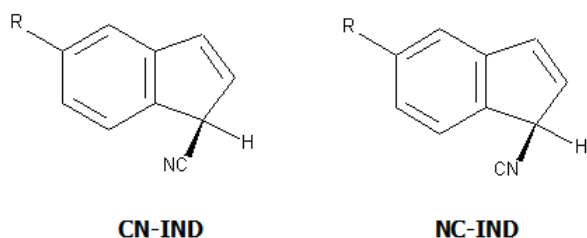
Scheme 1. Model compounds chosen for the study

The calculations were performed using Gaussian 09.[8] If a substituent was conformationally flexible, a set of starting conformations was generated by rotating sp^3-sp^3 and sp^3-sp^2 bonds with 120.0 torsion angle increments, and sp^2-sp^2 with 180.0. The geometries were optimized at the well-performing B3LYP/aug-cc-pvDZ level[9] with harmonic frequencies calculated so to ascertain the conformations are true minima. For molecules with flexible substituents, a population analysis was performed to exclude duplicates and calculate Boltzmann population factors. Then VCD spectra were simulated at the same level.

Out of many vibrational modes present in the calculated spectra, we decided to analyze only the best isolated ones: $\nu(CN)$, $\nu(NC)$ and $\nu(C^*H)$ stretching. Thus it was possible to avoid complications arising from vibrational coupling and problems in recognizing identity of modes. First, we inspected $\nu(CN)$ stretching mode in CN-IND which is located in the range of 2335-2343 cm^{-1}. Table S1 in Supporting Information provides computed spectral parameters of the mode along with the energetics of the CN-IND conformers under the study. In accordance with previous experimental and theoretical studies the frequencies and IR intensities have excellent linear correlations (Figure 1) with σ_p (r of 0.98 and -0.92 respectively).[10] We were also able to find an equally good correlation of VCD intensity with σ_p (r=0.94). It means that all these three quantities (frequency, IR and VCD intensity) are intercorrelated and this is to the best of our knowledge first such case ever reported in the literature.

An analogous mode in NC-IND is $\nu(NC)$ stretching which is present in the range of 2209-2211 cm^{-1}. Table S2 provides computed spectral parameters of the mode along with the energetics of the NC-IND conformers under the study. $\nu(NC)$ frequencies and IR intensities correlate nonlinearly with σ_p (r of 0.84 and 0.90 respectively, Figure S1, Supplementary Information). VCD intensity also followed the same trend as for $\nu(CN)$, however, the correlation is more qualitative. Even after exclusion of apparent outliers, r was about 0.75 (Figure S1).

In the case of $\nu(C^*H)$ stretching of methine in the chirality center of CN-IND the frequencies spanned in the region of 3004-3012 cm^{-1}. Table S3 provides computed spectral parameters of the mode along with the energetics of the CN-IND conformers under the study. Correlational analysis found nonlinear correlations of frequency and IR intensity with σ_p (r of 0.90 and 0.96 respectively) (Figure S2). VCD intensity exhibited here a strong nonlinear correlation with pEDA(I) parameter (r=0.97, Figure 2a).
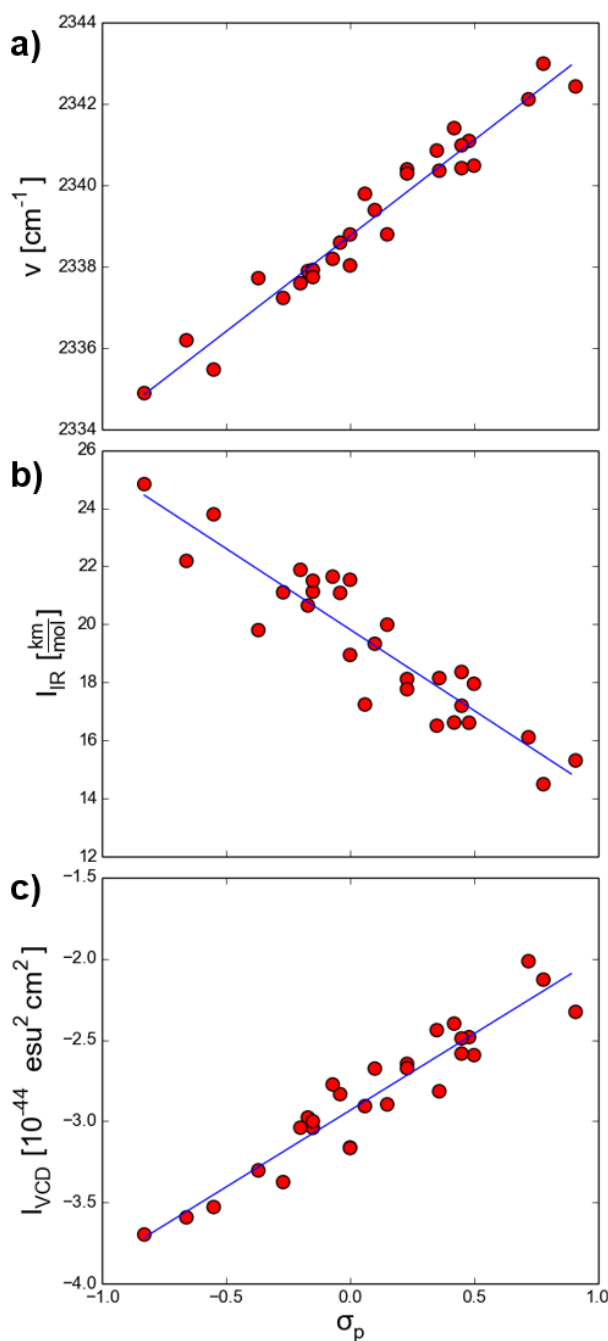
Figure 1. Correlations of $\nu(CN)$ spectral parameters a) ν = 4.70 (± 0.09) σ_p + 2338.77 (± 0.04), r= 0.98, n=28 b) I_{IR} = -5.57 (± 0.21) σ_p+ 19.83(± 0.09), r=-0.92, n=28 c) I_{VCD}= 0.94 (± 0.03) σ_p - 2.93 ± (0.01), r=0.94, n=28.

Interestingly, there was no significant correlation between frequency and σ_p in $\nu(C^*H)$ in NC-IND (Table S4). On the other hand, the latter two correlations (IR intensity with σ_p and VCD intensity with pEDA(I)) were equally good as previously (r of 0.97 and 0.97 respectively, Figure S3 and Figure 2b).
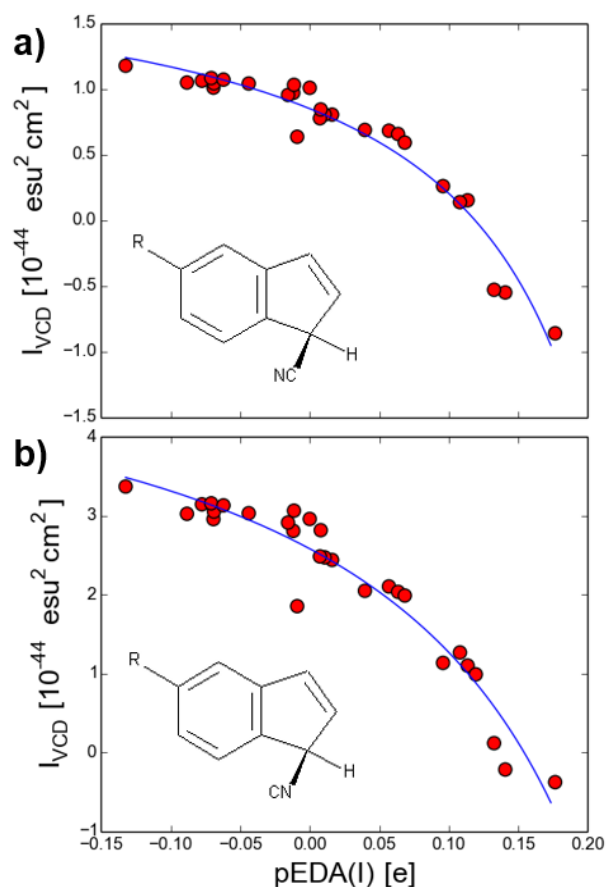
Figure 2. ν(C*H) VCD intensities in CN-IND and NC-IND exhibit strong nonlinear correlations with pEDA(I). a) I_{VCD} = (1+a* pEDA(I))/(b+c*x); a = -8.42 (± 0.28), b = 1.18 (± 0.04), c = -4.01 (± 0.36), r = 0.97, n = 27, – OMe excluded due to coupling of ν(C*H) in the chiral center with the ν(C*H) in OMe group. b) I_{VCD} = 1+(a*pEDA(I))/(b+c*x), a = -6.49 (± 0.20), b = 0.39 (± 0.01), c =-1.10 (± 0.16), r = 0.97, n = 28.

As seen in the above examples, VCD intensity can correlate with both considered substituent descriptors. σ_p might be said to describe change in electron density in the para-position of the benzene ring, while pEDA(I) is a theoretically derived measure of electronic change in the whole π-electron system of the compound, being in practice a measure of the resonance effect. Thus VCD intensity can depend on the overall substituent effect or its resonance component. The finding is analogous to the situation with IR intensity which can be sometimes modeled by original σ Hammett constants and in some cases by resonance effect σ_R Taft scale.[11]

In classical absorption (vibrational) spectroscopy the substituent effect can be observed in a change of band position and intensity. The former is associated with a force constant change of the corresponding normal mode and, to some extent, to a change of the mode anharmonicity as the substituent electron-donor-acceptor character alters, while the latter with the square of EDTM (electric dipole transition moment), in which the key factor is square of the second derivative of the dipole moment with respect to the normal mode coordinate.

In VCD, the band position is governed by the same rules as in IR, but the transition moment is a scalar product of EDTM and MDTM (magnetic dipole transition moment) vectors and thus rotational strength (to which VCD intensity is proportional) can be expressed as a product of three independent factors: values of EDTM and MDTM multiplied by the cosine of the angle ξ between the vectors:

$$R= | EDTM | | MDTM | \cos(\xi)$$

It was therefore interesting to see whether these factors alone might be correlated with the substituent effect descriptors (EDTM, MDTM, and cos(ξ) values for all considered modes are in Tables S5 and S6).

In the case of the ν(CN) in CN-IND, EDTM correlates well with σ_p (r=0.92, Figure S4) - which is obvious since EDTM is proportional to IR intensity correlating here as shown in Figure 1 – while MDTM and cos(ξ) do not correlate. The product of the latter two is nearly constant and this is why the VCD intensity is correlated here with the IR intensity.

The equation factors behave similarly in ν(NC) in NC-IND, with EDTM correlating well with σ_p (r=0.90) and no correlations found for MDTM and cos(ξ) (Figure S5)

A very interesting situation is observed for ν(C*H). In CN-IND both EDTM and MDTM correlate with σ_p (r=0.95, Figure S6 and r=0.91, Figure 3a, respectively), while pEDA(I), which excellently describes the VCD intensity of the mode, correlates with cos(ξ) (r=0.95, Figure 3b). The unprecedented correlation of pEDA(I) with cos(ξ) holds also for the vibration in NC-IND (r=0.95, Figure 3c), however here we cannot observe any correlation with MDTM (Figure S7).

To comment upon it, let us remind that for any achiral molecule cos(ξ)=0 and the EDTM and MDTM vectors are orthogonal. Increase of cos(ξ) as pEDA(I) decreases means that the more π-electron acceptor is the C5 substituent, the less orthogonal are the transition moment vectors (Figures 3b and 3c). Assuming that for the entire set of derivatives the amplitude of motions in the studied modes is similar, the more π-electron acceptor is the substituent the more chiral (asymmetrizing) is the mode.

The relationship in Figure 3a demonstrates that MDTM value decreases with increase of σ_p. This means that the overall substituent effect directly influences the velocity of changes of the magnetic moment connected with the mode.

In the ν(C*H) (Figure 2) we also observe a sign-change of a mode upon substituent exchange. The sign-change problem is an important issue in practical and theoretical VCD since its possibility adds further complication to interpretation of the VCD spectra and configuration assignments.[12] Until now substituent effect was not found among factors that can cause such a change as these were mainly: solvent effects, intermolecular interactions and the choice of an appropriate theoretical level for calculation. In practice, it is assumed that calculating VCD spectra of one of the derivatives should be enough for proper interpretation of VCD for its analogs, especially if substituents are far from the chiral center and do not interact with it.[13] We show here however that this way of proceeding might not always be right and a sign-change can occur even if the substituent is quite far from the chirality center. Even though it is probably quite a rare phenomenon, a researcher should be at least aware of its possibility.
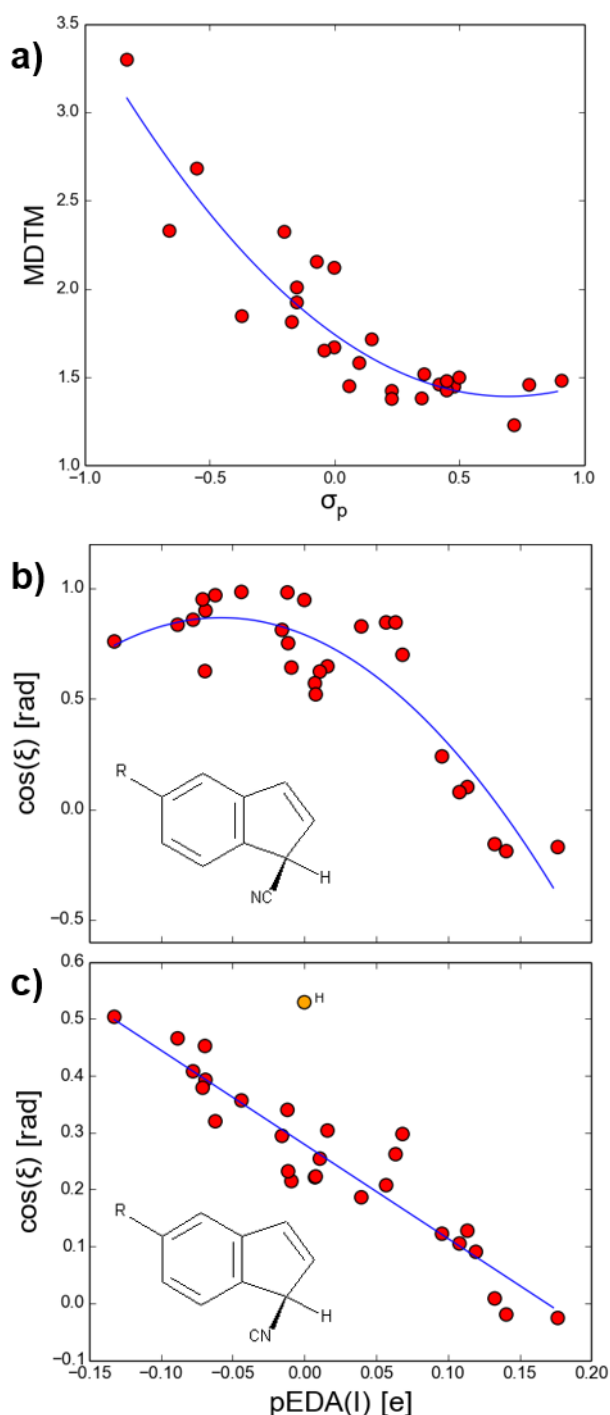
Figure 3. Correlations of ν(C*H) rotational strength factors with substituent effect scales. a) CN-IND, MDTM = 0.72 (± 0.17) σ_p^2 - 1.01 (± 0.09) σ_p + 1.74 (± 0.05), r = 0.91, n = 27 (OMe excluded) b) CN-IND, cos(ξ) = - 22.78 (± 5.00) pEDA(I)^2 - 2.65 (± 0.49) pEDA(I) + 0.79 (± 0.04), r = 0.90, n = 27 (OMe excluded) c) NC-IND, cos(ξ) = - 1.72 (± 2.02) pEDA(I)^2 - 1.59 (± 0.19) pEDA(I) + 0.30 (± 0.02), r = 0.90, n = 28.

Conclusions

In conclusion, we report here the first correlational study on substituent effect in vibrational circular dichroism. Strong correlations between VCD intensities of ν(CN) and σ_p, as well as between ν(C*H) and pEDA(I) were found, thus it can be stated that VCD intensities can – as is the case of IR intensities – be dependent on the overall substituent effect or only its resonance component.

Noticeably, ν(CN) frequencies, IR and VCD intensities in CN-IND are intercorrelated. We also present unprecedented correlations of MDTM and cos(ξ) values with substituent descriptors. The study brings also the case of a mode sign-change upon substituent exchange.

To understand better the nature of the substituent effect in VCD, a more thorough analysis is needed for systems 1) with a chiral group allowed to rotate 2) with various degrees of aromaticity 3) with non-continous conjugated bonds systems and 4) of different types of chirality (e.g. axial chirality). The issue of aromaticity is especially interesting in the light of an early-proposed ring current mechanism impacting VCD intensities.[14] Such a discussion goes beyond this Communication and is going to be presented in a series of following Regular Papers (including ongoing synthethic and experimental work).

Notes and references

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† Electronic Supplementary Information (ESI) available: Detailed spectral parameters of all considered modes, energetics of examined conformers, correlation plots of minor importance and coordinates of optimized structures. See DOI: 10.1039/c000000x/

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