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Interpretation of substituent-induced ^{13}C NMR chemical shifts of oxindoles†

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Based on the ^{13}C NMR chemical shifts of more than 300 oxindole derivatives, substituent-induced chemical shifts have been calculated for this family of compounds. These substituent effects have been compared to those of monosubstituted benzenes and the correlation with the Hammett σ values and dual substituent parameters has also been tested. By means of these validated substituent effects, the ^{13}C NMR chemical shifts of the oxindole skeleton containing various substituents can be accurately predicted.

Introduction

The importance of oxindole (1,3-dihydro-2*H*-indol-2-one, **1**, shown in Scheme 1) derivatives is indisputably shown by the large number of papers dealing with these compounds. The interest in oxindoles derives not only from the fact that they are immediate precursors of indoles but also from the varied biological activities displayed by members of this family. The oxindole skeleton can be found in herbicides[1] and many alkaloids (*e.g.*, horsfiline,[2] paraherquamide,[3] rhyncophylline,[4] Gelsemium alkaloids[5]), and its derivatives play a role as intermediates in the synthesis of indole alkaloids (*e.g.*, physostigmine[6]). However, the biological importance of this family is demonstrated most of all by drugs already marketed (*e.g.*, ropinirole,[7] ziprasidone[8]) and several new and promising oxindole derivatives used in various therapeutic fields.[9–12]

Over the past decade, high throughput has been one of the most important features in synthetic organic (combinatorial) chemistry and biological screening, which in turn requires high-throughput analytical and NMR techniques. In ACD's Combi NMR and similar software programmes, the automated prediction of ^{13}C chemical shifts becomes indispensable.[13]

The increasing interest in oxindoles necessitates an appropriate analytical background, a part of which is the exact assignment of the ^{1}H and ^{13}C NMR spectra. The large number of oxindole derivatives synthesised in our laboratory made the construction of a reliable database of ^{13}C NMR chemical shifts possible. We have measured the spectra of a series of mono- and polysubstituted oxindoles in order to gain information on the additivity of the substituent effects, and on the relationship between these effects and the electronic properties of the substituents. Using these well-grounded substituent effects it is possible to provide reliable assignments of carbon chemical shifts on the basis of simple 1D ^{13}C NMR spectra. The applied methods and the results obtained from this database are discussed below.

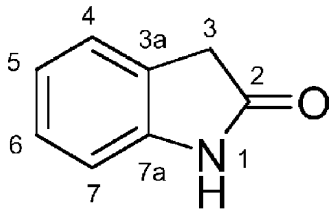
Results and discussion

Model building

After completing the NMR measurements of our oxindole chemical library, an overall search for published ^{13}C NMR data on oxindole derivatives has been conducted. In principle, oxindole (**1**) can exist in three tautomeric forms.[14,15] However, as stated in the literature,[14] each compound synthesised in our laboratory exists in the oxo form at C(2) in solution, exhibiting an sp^3 type C(3) carbon atom. On the other hand, isatins and oxindole derivatives with a double bond at atom C(3) show a different NMR behaviour, so these compounds (found in the literature) were not considered in our calculations. Since we intended to set up a database of general applicability, compounds containing very special substituents or an additional ring fused to the oxindole skeleton were also excluded. The remaining 254 oxindole derivatives together with the 105 compounds of our library (see Experimental) were divided into two parts: 315 of them were used in the model building and 44 randomly selected oxindoles were put aside for validation purposes.

The oxindole (**1**) skeleton can be substituted at 6 different positions: N(1), C(3), C(4), C(5), C(6) and C(7). The 315 compounds used in our model contain 85 different substituents in these 6 positions. Considering the different positions of the same substituent (*e.g.*, 5-F and 6-F), our calculations cover 128 substituents altogether. The 8 carbon signals [C(2), C(3), C(3a), C(4), C(5), C(6), C(7) and C(7a)] of all 315 compounds were assigned and collected in the form of substituent-induced chemical shifts (SCS). SCS_i^j can be defined in any monosubstituted oxindole (compound **n**) as the effect of the substituent *j* on the chemical shift of the carbon labelled *i* [C(*i*)], expressed in ppm units. Thus, SCS_i^j can be calculated as the difference between the chemical shift of the corresponding carbon atom in a monosubstituted oxindole (compound **n**) and the chemical shift of the same carbon in the parent oxindole (**1**).

In order to reduce the effects of intermolecular interactions on the chemical shifts, dilute solutions were used during the



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Scheme 1 Oxindole skeleton with the atom labels.

† Electronic supplementary information (ESI) available: full versions of Table 3 and Table 7. See http://www.rsc.org/suppdata/nj/b4/b403034f/

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measurements.[16,17] The NMR spectra of our derivatives and also those of oxindoles in the literature were measured at room temperature, mainly in $CDCl_3$. However, the chemical shifts of less soluble derivatives were determined in dimethyl sulfoxide-d_6, acetone-d_6, methanol-d_4 or acetonitrile-d_3. The literature is not consistent in the treatment of solvent effects. In the simplest case the derivatives are measured in different NMR solvents and the effect of the solvents on the chemical shifts is not considered.[18] For certain types of compounds, the insignificance of the choice of solvent has been proved.[19] However, the most accurate approach in evaluating the substituent effects is to use the chemical shifts of the parent molecule determined in the same solvent as the substituted compound.[20,21] For *O*-acyl glucoses, Yoshimoto *et al.* have clearly demonstrated that although the chemical shifts themselves slightly depend on the NMR solvent, the "acylation shifts" (the difference between the chemical shifts of the acylated and the non-acylated compound) are independent of it.[22] We have applied the same assumption for the SCS values of oxindoles. Hence, the definition of SCS_i^j in a monosubstituted oxindole (compound **n**) in any NMR solvent (solvent **A**) is as described in eqn. (1):

$$SCS_i^j = \delta_i \text{ (compound } \mathbf{n}\text{, solvent } \mathbf{A}) - \delta_i \text{ (}\mathbf{1}\text{, solvent } \mathbf{A}) \quad (1)$$

The ^{13}C NMR chemical shifts of oxindole (**1**) in the solvents mentioned above are shown in Table 1.

As a next step, we assumed the additivity of the individual substituent effects in the case of multiply substituted oxindole derivatives. In general, the additivity of SCS data can fail because of conformational movements[23a,24] and steric interactions of the substituents.[23b] Due to the conjugated π-electron system of the aromatic ring, the nonbonding electron pair of the nitrogen atom and the carbonyl group, the oxindole (**1**) skeleton is planar[14,25] and conformationally rigid. Accordingly, a multiple linear regression was carried out with the view to obtain the corresponding SCS values. If the multiply substituted oxindole (compound **s**) contains *m* substituents other than hydrogen on the oxindole skeleton, the ^{13}C NMR chemical shift of the carbon labelled *i* can be obtained as the sum of the chemical shifts of the same carbon in the parent oxindole (**1**) and the corresponding SCS values of the substituents [eqn. (2)]:

$$\delta_i(\text{compound } \mathbf{s}, \text{solvent } \mathbf{A}) = \delta_i(\mathbf{1}, \text{solvent } \mathbf{A}) + \sum_{j=1}^{m} SCS_i^j \quad (2)$$

It has to be emphasised that in the case of 3,3-disubstituted derivatives the SCS values of both substituents at the 3-position have to be considered in the calculation.

On the basis of eqn. (2), the SCS data have been calculated for the eight ring ^{13}C NMR signals of the 315 compounds involved in the model building. A multiple linear regression was carried out using the Statistica 6.0 software package.[26] The corresponding R^2 values for the model were definitely high, with the lowest value being 0.950 for C(3a) (Table 2, entry 1). However, we have subjected the residuals (ΣRes^2) to examination and have found a strikingly high value at C(3) (Table 2, entry 1), which led us to conclude that a few compounds should be omitted from the model. The most obvious outliers were the 3-monoacyl derivatives, owing to the presence of the double bond on C(3), leading to a tautomerisation of these compounds to either 2-hydroxy-1*H*-indoles[27] or to the corresponding 3-(1-hydroxyethylidene)oxindole derivatives.[28] After exclusion of the three 3-monoacyl compounds from the model, the multiple regression has been recalculated, resulting in a significant improvement of the R^2 values, particularly on C(3) (Table 2, entry 2). On the other hand, a second substituent at the C(3) position hinders the keto-enol tautomerism, such that 3,3-disubstituted derivatives show "ordinary" behaviour. Accordingly, these compounds could be used for the calculation of the SCS value of 3-acyl groups.

A systematic anomaly has been observed on C(6), which is found mostly in 5,6,7-trihalogenated oxindole derivatives. In these compounds, the total effect of the three electron-withdrawing substituents in mutually ortho positions is significantly less than the sum of the single SCS values.[23b] After omitting 5,6,7-trisubstituted oxindoles, the multiple regression was carried out again, resulting in the final model with even lower ΣRes^2 and high R^2 values (Table 2, entry 3).

When using published ^{13}C NMR data in the model building, some errors and incorrect assignments were found and corrected. Thus, the ^{13}C NMR signals of N–CH_3 and that of C(3) in 1-methyl-3-phenyloxindole and 3-(*tert*-butyl)-1-methyloxindole have been swapped,[29] and also the two carbonyl signals of 3-allyl-3-methoxycarbonyloxindole[30] have been swapped. The chemical shifts of C(3a) have been mistaken for those of C(7a) in the cases of both 3-bromomethyl-3-methyl-1-phenyloxindole and 3,3-dimethyl-1-phenyloxindole,[31] and the signals of C(7) and C(7a) have also been exchanged in 7-nitrooxindole.[32]

Finally, SCS data have been calculated for 128 different substituents. A set of selected data is shown in Table 3.[33] Using these, Table 1 and eqn. (2), the chemical shifts of any oxindole

Table 1 The ^{13}C NMR chemical shifts (ppm) of oxindole (**1**) in various NMR solvents

	C(2)	C(3)	C(3a)	C(4)	C(5)	C(6)	C(7)	C(7a)
Chloroform-d	178.0	36.3	125.3	124.6	122.3	127.9	109.8	142.5
Methanol-d_4	180.1	37.2	127.2	125.6	123.4	128.9	110.9	144.6
Dimethyl sulfoxide-d_6	176.6	35.9	125.9	124.5	121.3	127.6	109.3	143.9
Acetone-d_6	177.3	36.4	126.7	125.3	122.3	128.4	110.2	144.6
Acetonitrile-d_3	177.6	36.6	127.0	125.6	122.7	128.6	110.3	144.4

Table 2 Changes in the statistical values of multiple regression after each omission step[ab]

Entry	No. of compd		C(2)	C(3)	C(3a)	C(4)	C(5)	C(6)	C(7)	C(7a)
1[c]	315	R^2	0.961	0.977	0.950	0.990	0.997	0.990	0.989	0.969
		ΣRes^2	133.8	1340	258.8	153.7	158.3	256.3	77.45	103.3
2[d]	312	R^2	0.960	0.995	0.960	0.991	0.997	0.991	0.990	0.977
		ΣRes^2	132.2	289.3	199.0	146.0	149.4	246.2	74.84	78.17
3[e]	305	R^2	0.959	0.995	0.962	0.991	0.997	0.995	0.989	0.977
		ΣRes^2	130.3	288.2	186.5	145.2	143.7	117.8	74.51	76.14

[a] R is the multiple correlation coefficient. [b] ΣRes^2 is the sum of squares of differences between observed and predicted values. [c] For all 315 compounds. [d] After omission of 3-monoacyl derivatives. [e] After omission of 5,6,7-trisubstituted compounds.

Table 3 A selection of the calculated substituent-induced chemical shifts of oxindole derivatives[abc]

Entry	Substituent	C(2)	C(3)	C(3a)	C(4)	C(5)	C(6)	C(7)	C(7a)
1	1-Me	−2.37 s	−0.44 n	−0.25 n	−0.36 n	0.32 n	0.20 n	−1.65 s	2.87 s
2	1-Et	−3.46 s	−1.42 n	−0.30 n	−0.33 n	−0.10 n	−0.11 n	−1.59 s	1.83 s
3	1-Bu	−3.09 s	−1.29 n	−0.27 n	−0.54 n	1.65 s	1.35 n	−1.62 s	2.09 s
4	1-Ph	−2.66 s	−1.02 n	−0.49 n	0.00 n	0.55 n	−0.29 n	−0.61 n	2.53 s
5	1-Bn	−2.40 s	−0.66 n	−0.52 n	0.20 n	0.49 n	0.00 n	−0.66 s	1.83 s
6	1-$CH_2C{\equiv}CH$	−4.88 s	−2.52 s	−0.59 n	−0.31 n	0.16 n	−0.37 n	−0.91 n	1.13 s
7	1-CH_2OH	−2.14 s	−1.12 n	−0.92 n	−0.20 n	0.38 n	0.14 n	−0.59 n	1.10 n
8	1-Ac	−2.46 s	0.39 n	−1.86 s	0.23 n	1.70 s	0.27 n	6.64 s	−1.32 s
9	1-COOMe	−5.30 s	0.38 n	−2.25 s	0.41 n	0.45 n	1.82 s	5.25 s	−1.94 s
10	1-COOEt	−4.70 s	−0.53 n	−1.55 s	−0.45 n	1.72 s	0.88 n	5.30 s	−1.65 s
11	1-COOPh	−5.59 s	−0.46 n	−1.78 n	−0.01 n	0.78 n	2.39 s	5.82 s	−2.21 s
12	1-OH	−6.09 s	−2.74 s	−2.08 s	−0.43 n	0.33 n	0.04 n	−1.00 s	−0.32 n
13	3-Me	3.10 s	3.92 s	5.19 s	−0.81 s	0.28 n	−0.10 n	0.04 n	−1.27 s
14	3-Et	2.53 s	9.20 s	3.62 s	−0.71 s	0.24 n	−0.10 n	−0.06 n	−0.49 s
15	3-(*i*-Pr)	2.25 s	13.26 s	3.23 s	−0.04 n	−0.18 n	−0.10 n	−0.12 n	−0.25 n
16	3-Bu	2.59 s	9.03 s	3.82 s	−0.62 n	0.13 n	0.04 n	0.02 n	−0.59 n
17	3-(*i*-Bu)	3.04 s	7.58 s	4.30 s	−0.27 n	−0.38 n	−0.43 n	0.17 n	−0.29 n
18	3-(*t*-Bu)	1.94 s	14.63 s	3.06 s	2.96 s	−1.66 s	−1.90 s	−0.54 n	−0.33 n
19	3-(*c*-Hex)	2.60 s	13.97 s	3.67 s	0.57 n	0.27 n	0.20 n	0.27 n	0.07 n
20	3-Ph	1.03 s	13.29 s	4.39 s	0.65 s	0.19 n	0.18 n	0.41 s	−0.76 s
21	3-Bn	1.38 s	10.04 s	3.45 s	−0.23 n	−0.31 n	0.06 n	−0.01 n	−0.74 s
22	3-$CH_2C{\equiv}CH$	0.58 n	5.78 s	2.52 s	−0.65 n	0.25 n	0.33 n	0.02 n	−0.65 n
23	3-CH_2OH	1.33 n	10.90 s	1.62 n	−0.71 n	0.54 n	0.50 n	0.54 n	−0.29 n
24	3-OH	0.92 s	30.94 s	2.44 s	0.47 s	0.75 s	1.38 s	0.58 s	−0.95 s
25	3-CN	−7.84 s	1.48 n	0.97 n	0.48 n	1.15 n	−1.73 s	1.12 s	−1.13 s
26	3-Ac	−2.01 s	34.42 s	1.53 n	1.52 n	2.06 s	0.51 n	2.36 s	−0.96 n
27	3-COOMe	−8.11 s	14.99 s	0.20 n	−3.13 s	5.84 s	1.68 n	8.53 s	−2.13 s
28	3-OAc	−2.85 s	34.98 s	1.70 n	−1.37 n	−0.45 n	0.81 n	−0.07 n	−0.23 n
29	3-OMe	−1.98 s	36.53 s	0.35 n	−0.02 n	0.58 n	−0.01 n	0.29 n	−0.99 s
30	3-SMe	−0.30 n	8.79 s	0.85 s	0.42 n	0.81 s	1.13 s	0.35 n	−0.93 s
31	3-Cl	−3.42 s	17.70 s	1.49 s	0.56 s	1.17 s	2.07 s	0.95 s	−1.74 s
32	3-Br	−2.47 s	10.18 s	1.70 s	0.20 n	0.68 n	0.83 n	0.90 n	−0.71 n
33	3-N_3	−2.71 s	22.33 s	1.63 n	0.40 n	0.66 n	−1.25 n	0.79 n	−0.67 n
34	4-Me	−0.18 n	−0.81 n	−1.48 n	10.13 s	0.00 n	−0.08 n	−2.59 s	−0.21 n
35	4-CH_2OH	0.08 n	−0.60 n	−2.23 s	13.86 s	−0.93 n	0.24 n	−0.60 n	0.22 n
36	4-COOH	−0.69 n	1.42 n	−0.21 n	2.71 s	1.83 n	0.29 n	2.78 s	0.74 n
37	4-CN	−1.38 n	−0.61 n	3.27 s	−16.53 s	3.85 s	1.30 n	4.43 s	0.95 n
38	4-Cl	−0.58 n	−1.29 n	−2.15 n	5.47 s	−1.18 n	1.16 n	−1.08 n	1.20 n
39	4-Br	−1.64 s	2.85 s	−3.72 s	−0.84 n	1.42 n	−7.28 s	−3.10 n	2.19 s
40	4-I	−1.69 n	4.32 s	2.98 s	−32.02 s	4.54 s	3.39 s	−0.92 n	0.84 n
41	4-OMe	−0.35 n	−1.82 n	−12.48 s	34.52 s	−13.06 s	1.57 s	−6.78 s	1.17 s
42	4-NO_2	−1.10 s	0.74 n	−3.33 s	20.47 s	−4.33 s	1.47 s	5.66 s	2.31 s
43	5-Me	−0.24 n	−0.34 n	0.55 n	0.61 s	9.26 s	0.20 n	−0.28 n	−2.34 s
44	5-Ac	−0.12 n	−2.29 s	0.08 n	0.18 n	9.25 s	2.08 s	−0.41 n	5.38 s
45	5-COOMe	0.21 n	−0.54 n	0.70 n	0.45 n	0.41 n	1.46 n	−0.21 n	4.44 s
46	5-CN	−0.53 n	−0.91 n	1.49 s	3.34 s	−17.60 s	5.43 s	0.80 n	4.22 s
47	5-F	−0.48 n	−0.08 n	1.12 s	−11.70 s	36.18 s	−13.10 s	0.60 s	−3.41 s
48	5-Cl	−0.89 s	−0.56 n	1.49 s	0.10 n	5.68 s	−0.56 s	1.17 s	−1.26 s
49	5-Br	−0.90 s	0.61 n	2.29 s	3.17 s	−7.27 s	3.19 s	1.49 s	−0.96 s
50	5-OMe	−0.35 n	0.13 n	0.96 s	−14.23 s	33.78 s	−14.95 s	2.27 s	−6.59 s
51	5-NO_2	−0.28 n	−0.95 n	0.79 n	−4.11 s	21.72 s	−2.75 s	0.09 n	5.35 s
52	5-NH_2	−0.98 n	−0.22 n	0.34 n	−12.60 s	22.30 s	−14.61 s	0.43 n	−10.04 s
53	5-SO_2Cl	−0.57 n	−0.25 n	2.13 s	−1.39 s	16.27 s	0.94 n	0.50 n	6.18 s
54	5-SO_2NH_2	−0.43 n	−1.02 n	−0.29 n	−2.16 s	16.29 s	−0.67 n	−0.01 n	3.16 s
55	6-Me	0.12 n	−1.08 n	−1.84 n	−1.29 n	0.82 n	11.61 s	0.63 n	−0.52 n
56	6-F	0.37 n	−0.52 n	−4.48 s	0.86 n	−13.52 s	34.33 s	−11.11 s	1.20 s
57	6-Cl	0.06 n	−0.73 n	−1.00 n	−0.07 n	0.06 n	3.50 s	0.13 n	1.42 s
58	6-Br	−1.13 n	−1.21 n	−1.38 n	−0.94 n	2.62 s	−3.48 s	3.76 s	0.70 n
59	6-OMe	0.63 n	−0.22 n	−10.35 s	−1.17 n	−14.45 s	32.95 s	−13.92 s	1.04 s
60	6-NO_2	−1.25 n	1.23 n	7.08 s	0.55 n	−4.34 s	20.42 s	−5.24 s	1.14 s
61	7-Me	0.32 n	0.46 n	0.01 n	−2.71 s	0.45 n	1.40 s	9.54 s	−1.94 s
62	7-(*t*-Bu)	−0.39 n	−1.75 n	1.33 n	1.80 n	−0.19 n	4.44 s	10.62 s	−2.54 s
63	7-Cl	−0.43 n	0.83 n	2.24 s	−1.60 s	2.07 s	2.20 s	4.44 s	−2.93 s
64	7-Br	0.73 n	0.25 n	5.18 s	3.98 s	−2.32 s	−0.15 n	−6.32 s	−8.26 s
65	7-OMe	0.00 n	1.97 n	2.19 s	−12.97 s	1.06 n	−10.62 s	34.87 s	−10.49 s
66	7-NO_2	−0.18 n	−1.71 n	3.84 s	6.03 s	0.25 n	−5.13 s	21.41 s	−3.76 s
67	7-CF_3	0.36 n	−3.79 s	2.22 n	0.56 n	4.87 s	−3.25 s	11.76 s	−2.69 s

[a] All SCS values are given in ppm units. [b] In the cells, 's' indicates that the effect of the substituent is significant for the carbon chemical shift ($p < 0.05$). [c] In the cells, 'n' indicates that the effect of the substituent is not significant for the carbon chemical shift ($p > 0.05$).

derivative can be calculated, provided the substituents can be found in Table 3.

In the early years of NMR, the biological interest in oxindoles prompted the initiation of a similar study.[20] Gassman and co-workers calculated the SCS values for a limited set of substituents (OMe, Me, Cl, COOEt, CN, NO_2) on the aromatic ring. In their study, only the effects on the aromatic nucleus were considered. Furthermore, ipso, ortho, meta and para SCS values were determined, independently of the exact position of the substituent. Our results indicate that this latter simplification may depreciate the accuracy of the prediction: for example, the ipso effect of the methyl group shows large differences depending on the position of the substituent (11.61 ppm for 6-Me and 9.54 ppm for 7-Me). On the other hand, the SCS of the 5-OMe group for C(6) is rather similar to that of the 6-OMe group for C(5) (−14.95 and −14.45 ppm, respectively). Consequently, if a certain substituent on the aromatic ring cannot be found in Table 3, the values of the same group in a different position can be used instead as a simple but less accurate alternative.

A further analysis of the substituent effects has shown that the sequence of the substituent effects at the ipso carbon atoms is identical with that of the electronegativity values of the simple non-alkyl substituents: $I < CN < Br < Cl < SO_2X < NO_2 < NH_2 < OEt < OMe < F$.[34] This statement is equally true for C(4), C(5), C(6) and C(7).

In the case of alkyl substituents on C(3), the effect at the ipso carbon correlates with the order of the alkyl groups:[23c] primary < secondary < tertiary alkyl groups (Table 3, entries 13–19). Substituents on C(3) that exhibit a −I or a +M effect (entries 25–33) and also substituents on N(1) (entries 1–12) caused an upfield shift of the C(2) carbon atom signal.

Comparison with monosubstituted benzenes and 4-substituted acetanilides

Aromatic compounds have always played a central role in the investigation of substituent-induced perturbations of σ- and π-electron distributions and of the way this is reflected in physical and chemical properties. Therefore, we have made a comparison between our calculated SCS values and the corresponding SCS's for monosubstituted benzenes available in the literature[35] and have found a satisfactory correlation between the two sets of data. For example, the SCS values of the fluorine atom in monosubstituted benzenes are: +34.75 (ipso), −12.97 (ortho), +1.58 (meta) and −4.41 (para) ppm. The corresponding SCS values for the 6-F substituent in oxindoles (Table 3, entry 56) are as follows: +34.33 (ipso), −11.11 and −13.52 (two ortho carbons), +1.20 and +0.86 (two meta carbons) and −4.48 (para) ppm.

The statistical calculation of the correlation was carried out for C(4), C(5), C(6) and C(7) with all substituents. The results in Table 4 show a good correlation for ipso, ortho and para carbon atoms in the cases of C(4), C(5) and C(6). However, no correlation has been found for meta carbons. Similarly, only very poor correlations have been observed in each position for C(7), the reason for which being the special behaviour of C(7) in the oxindole skeleton. While C(4), C(5) and C(6) are usual "benzene-type" carbon atoms, C(7) is much more shielded.[23d]

Acetanilides show a closer structural analogy to oxindoles than monosubstituted benzenes. A comparison of the oxindole C(5) SCS values with the SCS's of 4-substituted acetanilides[36] showed a similar trend: excellent correlations ($R^2 > 0.995$) have been observed for ipso, ortho and para carbons.

Hammett σ analysis of the SCS data

Several methods have been used to provide an insight into the mechanism of the transmission of electronic effects within the molecular system. There are also different theories for the discussion of substituent effects on the ^{13}C NMR chemical shifts. Recently, Wiberg *et al.* have made important contributions in this field, using *ab initio* calculations of nuclear shieldings for acetylenes[37] and small fluorine-containing molecules.[38] In the case of aromatic compounds, however, one of the most widely used means for the study of substituent effects is the Hammett equation. Among the number of papers discussing the Hammett σ parameter, we have chosen the general work of Hansch and co-workers.[39]

A correlation has been sought between the Hammett σ_m and σ_p parameters[39] and the corresponding SCS values of the oxindole skeleton. According to our calculations, there is an acceptable agreement ($R^2 > 0.8$) with the para Hammett values (σ_p), the only exception being C(7): once again this carbon atom exhibits special behaviour. On the other hand, practically no correlation could be observed between our substituent-induced chemical shifts and the σ_m values ($R^2 < 0.5$). Thus, similarly to substituted benzenes,[35] the meta carbon SCS's in oxindoles do not show a close parallel with σ_m.[23e]

Dual substituent parameter (DSP) analysis of the SCS data

Following Hammett's success, efforts were made to split the electronic effect of a substituent into field (inductive) and resonance components. In our analysis, Swain and Lupton's σ_F and σ_R parameters have been used to represent the substituent properties and the dual substituent equation [eqn. (3)] has been applied:

$$SCS_i = \rho_F \sigma_{F,i} + \rho_R \sigma_{R,i} + c \qquad (3)$$

In eqn. (3), σ_F and σ_R are, respectively, the field and resonance substituent constants, ρ_F and ρ_R are the relevant susceptibility coefficients and c represents the intercept of the regression plane with the SCS axis.[40]

In ipso, ortho and meta positions of the oxindole skeleton, only poor correlations have been found with σ_F and σ_R. On the other hand, a reasonable correlation ($R^2 > 0.96$) has been detected in the case of the para positions except for the "refractory" carbon atom C(7) (Table 5). According to the data in Table 5, $\rho_R > \rho_F$ for all para carbon atoms, which indicates a large resonance contribution in the transmission of electronic effects within the oxindole skeleton. Resonance factors are clearly less important for σ_m than for σ_p because conjugation is not as complete for a meta substituent.[41] This

Table 4 Comparison with the SCS values of monosubstituted benzenes

	C(4)		C(5)		C(6)		C(7)	
Position	Carbon	R^2	Carbon	R^2	Carbon	R^2	Carbon	R^2
ipso	C(4)	0.991	C(5)	0.995	C(6)	0.984	C(7)	0.773
ortho	C(3a)	0.828	C(4)	0.996	C(5)	0.991	C(6)	0.250
	C(5)	0.954	C(6)	0.972	C(7)	0.996	C(7a)	0.635
meta	C(6)	0.355	C(3a)	0.639	C(4)	0.668	C(5)	0.576
	C(7a)	0.062	C(7)	0.520	C(7a)	0.214	C(3a)	0.046
para	C(7)	0.949	C(7a)	0.990	C(3a)	0.966	C(4)	0.617

Table 5 Dual substituent parameter analysis of the SCS data for para carbon atoms[a]

Position of substitution	para Carbon	ρ_F[b]	ρ_R[c]	R^2
C(4)	C(7)	4.82	15.17	0.963
C(5)	C(7a)	5.09	15.04	0.984
C(6)	C(3a)	3.39	22.89	0.993
C(7)	C(4)	1.21	19.49	0.608

[a] σ_F and σ_R data were taken from ref. 39. [b] Field susceptibility coefficient. [c] Resonance susceptibility coefficient.

explains why the oxindole SCS's resulted in satisfactory correlations only with the Hammett σ_p.

Validation

As mentioned above, prior to the calculation of the SCS data, 44 randomly selected oxindole derivatives were left out from the model building, so that they could be used for external validation of the model. We have calculated the ^{13}C NMR chemical shifts of these 44 compounds for each carbon and have represented the measured ^{13}C NMR chemical shifts as a function of the predicted ones. The comparison shows excellent agreement, which is illustrated in Fig. 1 by the fitting of the measured data points of two selected carbon atoms, C(5) and C(6). The calculated and measured values are in most cases within a ±1.5 ppm range for all eight carbons, which allows a reasonable prediction of the ^{13}C NMR shifts and an accurate assignment of the single carbon signals without 2D measurements.

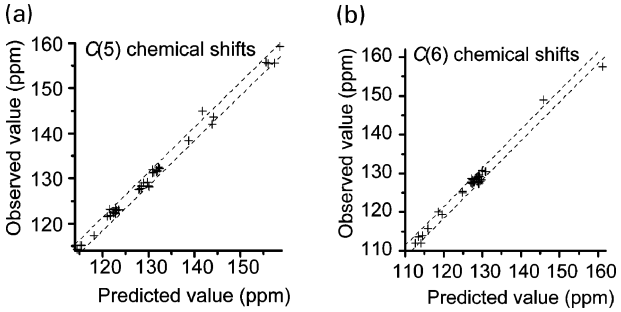

Fig. 1 Predicted *vs.* observed ^{13}C NMR chemical shifts with a ±1.5 ppm range.

In the case of the few outlier elements the pure additivity rule is slightly violated. When strongly electron-withdrawing substituents on an aromatic ring are in mutually ortho positions, the total effect of the two substituents is less than the sum of the single SCS values, as mentioned above. The outlier element under the fitted line in Fig. 1(b) has a greater predicted value for C(6) than the observed one. This molecule is 5-chloro-3-(4-chlorobutyl)-3-ethyl-6-flurooxindole; the two electron-withdrawing substituents (5-Cl, 6-F) on the aromatic ring are in ortho positions to each other. 1-Butyl-5,6-dimethoxyoxindole represents the inverse case: due to the electron-donating substituents the observed value is higher than the predicted one for both C(5) and C(6) (Fig. 1).

The C(3) position differs significantly from the others since this is the only carbon in the sp^3 hybrid state, so the oxindole skeleton can bear two different substituents in this position. Contrary to expectations, we have not experienced any violation of the additivity rule in this position, neither in the case of two strongly electron-withdrawing substituents (*e.g.*, 3,3-dichloro derivatives), nor in the case of two sterically bulky substituents (*e.g.*, 3,3-diphenyl derivatives).

In order to check the goodness of the validation, we have evaluated the characteristic statistical indicators. As expected, the slopes (a) of the fitted straight lines are close to unity and excellent R^2 values have again been obtained (Table 6).

Beside R^2, a further criterion to establish the robustness and the predictive ability of a model is q^2. For the carbon labelled i, the definition of q^2 is given by eqn. (4):

$$q_i^2 = 1 - \frac{\sum_{k=1}^{44} \left(\delta_i^k - \ddot{\delta}_i^k\right)^2}{\sum_{k=1}^{44} \left(\delta_i^k - \bar{\delta}_i\right)^2} \qquad (4)$$

where δ^k is the measured carbon chemical shift, $\ddot{\delta}^k$ is the predicted carbon chemical shift and $\bar{\delta}$ is the mean value of all measured carbon chemical shifts in the model. A high value of this statistical characteristic ($q^2 > 0.5$) is often considered as proof of the high predictive ability of the model. A recent publication has demonstrated that in the case of a leave-one-out (LOO) internal cross-validation, q^2 appears to be a necessary but not sufficient condition for the model to have a high predictive power: external validation is the only way to establish a good model.[42] As described above, we have performed an external validation, so the high values of q^2 shown in Table 6 together with the high R^2 values are marks of an extraordinarily reliable model.

Conclusions

We have aimed at setting up a reliable model for substituent-induced chemical shifts of oxindoles, a family of significant biological impact. For this purpose, an overall literature search was conducted for published ^{13}C NMR data. In addition, several new oxindole derivatives have been synthesised in our laboratory. Taken together, more than 300 molecules served as a database for our calculations.

Due to the rigidity of the oxindole skeleton, the additivity of the substituent shifts was expected. Indeed, the regression resulted in a good model, which indicates that our expectations regarding the additivity of the single substituent effects were correct. Our SCS data have been compared to the substituent effects of monosubstituted benzenes, and correlations with the Hammett σ values and the dual substituent parameters have also been performed. An external validation

Table 6 Characteristic statistical values of the external validation

	C(2)	C(3)	C(3a)	C(4)	C(5)	C(6)	C(7)	C(7a)
a[a]	0.99	1.00	0.99	1.00	0.99	0.99	0.99	1.00
ΣRes^2	17.5	39.2	26.1	25.0	33.0	51.0	16.3	14.1
R^2	0.960	0.994	0.966	0.985	0.995	0.981	0.974	0.973
q^2	0.965	0.994	0.968	0.985	0.995	0.980	0.967	0.966

[a] Slope of the fitted straight line.

established the outstanding reliability of the calculated substituent shifts. Taking advantage of the SCS data, we have re-analysed the incorrectly assigned ^{13}C NMR signals found in the literature.

By means of the calculated SCS values, the assignment of the ^{13}C NMR signals of oxindole derivatives can be carried out in a partly automated manner, without 2D measurements. This validated data set can also be of great value in predicting ^{13}C NMR parameters and it can be applied as an enlargement of the database of spectrum assignment software.

Experimental

Synthesis

3-Hydroxyoxindoles and oxindoles unsubstituted in the 3-position were synthesised by Raney nickel-catalysed hydrogenation of isatins.[43] The 3-(ω-hydroxyalkylated) and most of the 3-monoalkylated compounds were prepared using a method (Raney nickel-induced alkylation of oxindoles with alcohols and diols) elaborated at our laboratory.[44,45] In addition to the 18 compounds described in refs. 44 and 45, a further 87 oxindole derivatives have been synthesised. Most of these compounds are not reported in the literature; others have been published, albeit without ^{13}C NMR data. The 3,3-disubstituted and 1,3,3-trisubstituted oxindoles were prepared analogously to the known alkylation methods.[46] Electrophilic substitutions on the aromatic ring[47] and acylations on the nitrogen atom[48] were carried out using standard procedures. For 30 selected derivatives, the ^{13}C NMR chemical shifts of the skeleton atoms are listed in Table 7. The full table contains all 87 compounds, including the chemical shifts of the substituents as well.[33]

NMR spectra

All spectra were recorded at 298 K on a Varian Unity Inova 400 spectrometer at 400 MHz for ^{1}H and 100 MHz for ^{13}C nuclei. The NMR spectra of our compounds were acquired in $CDCl_3$ or DMSO-d_6. The ^{1}H NMR spectra were internally referenced to TMS; the ^{13}C NMR spectra were internally referenced to the deuterium-coupled carbon signal of the solvents (77.0 ppm for $CDCl_3$ and 39.7 ppm for DMSO-d_6). A 5 mm multinuclear ID PFG probe (with *z*-gradient) was used for the standard 1D and 2D (COSY, HMQC, HMBC) experiments. 1D proton decoupled ^{13}C spectra were recorded under the following conditions: 45.0° pulse, 25 000 Hz sweep width, 1.3 s acquisition time; 8000 to 16 000 scans of 64 K data points were accumulated and zero-filled to 128 K. The relaxation delay was 1.7 s (or 3.0 s in the case of compounds containing one or more fluorine atoms). The ^{13}C FID signals were subjected to Fourier transformation using 1 Hz line broadening. Samples were prepared by dissolving 20–25 mg of the corresponding compound in 800–900 μl of the appropriate solvent.

When necessary, 2D NMR measurements were used for the structure determination of derivatives synthesised in our laboratory. The 2D homonuclear ^{1}H–^{1}H correlation spectra (COSY) and the heteronuclear ^{13}C–^{1}H correlation spectra (HSQC, HMBC) were recorded using the standard Varian software. The GHSQC spectra were measured in the phase-sensitive mode and with magnetic field gradients. The GHMBC spectra were processed in the magnitude mode. The multiple-bond couplings were set to 8 Hz; 256 time increments were collected for each data set and they were zero-filled to 512.

Table 7 ^{13}C NMR chemical shifts of selected compounds[a]

	Substituent[b,c]						^{13}C NMR δ (oxindole skeleton)							
Entry	N(1)	C(3)	C(3)	C(5)	C(6)	C(7)	C(2)	C(3)	C(3a)	C(4)	C(5)	C(6)	C(7)	C(7a)
1	2,6-diCl-C_6H_3	*i*-Pr					175.8	51.7	130.5	124.7	122.7	127.7	108.8	142.8
2	Bn	OH					177.4	69.8	127.1	125.2	123.2	129.6	109.5	142.9
3	Ac	Et	Et	SO_2Cl			179.8	55.0	133.2	121.1	140.7	128.2	116.9	145.9
4	COOEt	Et					175.8	46.9	127.6	123.5	124.3	128.0	114.9	139.9
5	Me	$CH_2C{\equiv}CH$	Et				178.5	51.5	130.9	122.4	123.2	128.1	107.7	143.8
6	Me	Et	Et	Br			179.3	54.6	134.2	125.9	115.1	130.4	109.0	143.4
7	CH_2OH	CH_2OH	Et				179.7	56.2	129.5	122.9	123.1	128.3	109.5	142.6
8	$CH{=}CH_2$	Et	Et				179.4	53.9	131.7	123.1	122.9	127.5	109.3	142.1
9	$CH{=}C{=}CH_2$	$CH_2C{\equiv}CH$	Et				177.0	50.8	131.1	123.1	123.3	128.2	110.6	141.7
10[d]		*i*-Pr	OH				179.7	78.4	130.8	124.8	121.4	128.9	109.5	142.4
11		*c*-Hex					180.4	52.1	128.6	124.6	122.1	127.7	109.7	141.9
12		CH_2Ac					179.7	44.2	129.4	124.4	122.5	128.1	109.7	141.3
13		Bu					181.2	46.3	129.9	124.0	122.1	127.7	109.8	141.8
14		$(CH_2)_3OH$					180.2	45.5	129.5	124.1	122.5	127.9	109.6	141.3
15		$(CH_2)_4OSO_2Me$				Me	180.8	46.1	128.8	121.2	122.2	128.8	119.3	140.4
16		$(CH_2)_5OSO_2Me$		F			180.5	46.3	131.0	111.7	158.8	114.0	110.3	137.6
17[d]		$(CH_2)_4Br$					178.9	45.1	129.7	124.1	121.4	127.7	109.3	142.9
18		Et		NO_2			179.3	46.2	130.6	119.8	142.1	125.3	109.2	149.8
19		Et		SO_2Cl			179.8	46.9	130.7	123.1	138.2	128.8	109.8	148.0
20[d]		Et	*i*-Pr				182.5	57.6	131.5	123.9	122.0	127.5	109.3	141.6
21		Et	Bn				181.7	55.8	131.4	123.8	122.0	127.7	109.5	141.1
22		Et	$(CH_2)_4OH$				181.9	54.1	132.5	123.1	122.5	127.6	109.3	141.0
23		Et	Et	Br			182.6	55.4	134.7	126.2	115.1	130.5	111.2	140.7
24		Et	Et	Ac			183.4	55.0	132.8	122.9	132.0	129.8	109.1	146.3
25[d]		Et	Et	NH_2			180.4	54.1	132.7	110.2	143.6	112.8	109.4	132.9
26		Et	Et	Cl		Cl	180.4	56.5	135.2	122.0	128.1	127.4	115.1	137.8
27		Et	$(CH_2)_3Cl$	Cl			182.1	54.1	133.9	123.5	128.1	128.0	110.8	139.8
28[d]		Et	$(CH_2)_4Cl$	SO_2NH_2			181.0	53.4	132.6	120.9	137.6	126.6	109.1	145.7
29		Et	$(CH_2)_4Cl$	F		Cl	180.6	55.8	134.9	109.7	158.8	114.8	114.8	135.1
30		Et	$(CH_2)_5Br$		F		183.3	53.9	127.7	123.8	108.7	162.4	98.4	142.5

[a] Solvent: $CDCl_3$ unless stated otherwise. [b] Indicated if different from hydrogen. [c] The substituent on C(4) is hydrogen in each compound. [d] Solvent: DMSO-d_6.

Statistical calculations

The multiple linear regressions were carried out using the least-squares estimation in the Statistica 6.0 software package.[26] We used the standard method for the multiple regression, which means that the effect of all independent variables to the dependent variable was considered at the same time. The intercept was included in the model, meaning that the regression straight line was not forced through the origin. The tolerance was set to a default value of 0.01. By means of this small value we could avoid identical variables in the equations. The level of significance (p) was set to 0.05. In many areas of research, this p-level is customarily treated as an upper "borderline acceptable" error level.

The SCS data have been calculated for 128 different substituents. The statistical significance of the model is excellent. In general, results that are significant at the $p < 0.001$ level are often called "highly" significant. In our model the value of "p" was less than 0.0001 for all eight carbon atoms.

Our model proved to be reliable so a correlation of calculated *vs*. measured chemical shifts should not show any constant deviation. Thus, the correlation was constrained to have zero intercept during the validation.

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