Calculation of the Nucleophilic Superdelocalizability by the CNDO/2 Method

Keyphrases □ Structure–activity relationships—calculation of the nucleophilic superdelocalizability by the CNDO/2 method, perturbation theory □ Perturbation theory—calculation of the nucleophilic superdelocalizability by the CNDO/2 method, structure–activity relationships □ Nucleophilic superdelocalizability—calculation by the CNDO/2 method, perturbation theory, structure–activity relationships

To the Editor:

In the application of the perturbation theory to the search of structure–activity relationships (1–3), there is an approximation that consists of replacing energies of the virtual molecular orbitals of the receptor by a constant. This replacement, expressed in previous reports (1, 4), leads to the appearance of the nucleophilic superdelocalizability index, S^N, of the atoms of a drug, in the expression relating the equilibrium constant to molecular structure factors. This index is usually calculated with semiempirical methods, like CNDO/2[1] (3) or INDO (2). The S^N index of the atom p is defined as:

$$S_p^N = 2 \sum_n \sum_j^{AO} \frac{C_{jn}^2}{E_n} \qquad \text{(Eq. 1)}$$

where n is the virtual molecular orbitals, E_n is the energy of the nth virtual molecular orbital, the summation on j is over the atomic orbitals (AO) of the atom p that contribute to the basis, and C_{jn} is one Linear Combination of Atomic Orbitals (LCAO) coefficient.

For one N electron system with a basis of t AOs, the CNDO/2 method produces $N/2$ occupied molecular orbitals and $(t - N/2)$ virtual molecular orbitals. These virtual molecular orbitals cannot be regarded as suitable for the description of the excited states of the system.

With the aim of examining the dependence of the CNDO/2 S^N values on the conformation, we have analyzed the value of this index for several rotamers in a group of molecules. Presented here are the results for the amine nitrogen and the carbon atom where the hydroxide group is attached, for six rotamers of the p-hydroxy-β-phenylethylamine in its basic and protonated form (Table I). For comparison, we present also the net charges and the electrophilic superdelocalizabilities of these atoms. The relative positions of the hydroxide group and the amine chain are referred to by *cis* and *trans*; parallel (//) and perpendicular ($\perp$) refer to the position of the substituents in relation to the phenyl ring. The geometry employed is composed of bond angles and bond distances normally found in crystallographic studies.

From Table I it can be seen that the values of Q and S^E do not change significantly between the different rotamers in the basic and protonated forms. The S^N index does not change in the basic rotamers; the protonated rotamers show profound changes, but these do not seem to show any relation with the conformation. Negative S^N values are due to the appearance of virtual molecular orbitals with negative energies.

Table I—Reactivity Indexes of the Nitrogen and Carbon (Hydroxide) Atoms of some Rotamers of the p-Hydroxy-β-Phenylethylamine

Form	Position of the —OH and Ethylamine Groups[a]	Q_c	S_c^E	S_c^N	Q_N	S_N^E	S_N^N
Basic							
	N //, O $\perp$	0.1588	−4.6864	13.2226	−0.2502	−7.0713	7.1340
	cis, N $\perp$, O $\perp$	0.1542	−4.7115	13.0695	−0.2477	−7.0288	7.2308
	trans, N $\perp$, O $\perp$	0.1542	−4.7120	13.0661	−0.2477	−7.0328	7.2234
	cis, N //, O //	0.1653	−4.6548	13.2010	−0.2502	−7.0740	7.1292
	trans, N //, O //	0.1655	−4.6549	13.1981	−0.2502	−7.0761	7.1255
	N $\perp$, O //	0.1609	−4.6802	13.0521	−0.2477	−7.0364	7.2158
Protonated							
	N //, O $\perp$	0.1816	−3.9527	84.9492	−0.0275	−3.9295	−81.9167
	cis, N $\perp$, O $\perp$	0.1810	−3.9575	−8.1637	−0.0268	−3.9247	−331.5201
	trans, N $\perp$, O $\perp$	0.1809	−3.9588	−15.6034	−0.0268	−3.9258	−409.2566
	cis, N //, O //	0.1878	−3.9273	54.8285	−0.0275	−3.9299	−371.0407
	trans, N //, O //	0.1877	−3.9281	44.8999	−0.0274	−3.9307	−563.3219
	N $\perp$, O //	0.1877	−3.9330	−32.9728	−0.0268	−3.9265	−621.9106

[a] The symbols // and $\perp$ indicate parallel and perpendicular positions, respectively, in relation to the phenyl ring.

Table II—S^N Value for the Nitrogen Atom in Some β-Phenylethylamines

Substituent	S^N
o—OCH_3	780.0266
m—OCH_3	77.0958
p—OH	−371.0407
p—CH_3	586.3877
—H	−302.6347

In Table II we present the S^N values for the nitrogen atom in a group of protonated β-phenylethylamines. All of the substituents are coplanar with the phenyl ring. Even so, the nitrogen S^N values seem to show no relation with the substitution.

Perhaps this lack of correlation between S^N and molecular structure in protonated molecules could explain why in some quantum chemical studies the S^N indexes do not appear, or, when they do, their t values are low.

This analysis strongly suggests that the S^N values obtained with the CNDO/2 method must be employed with caution in structure–activity studies.

Considering that a great number of molecules act in a protonated form and that the exact position of the substituents at the receptor level is not known, it seems necessary to define an S^N index that shows the same dependence on the conformation as the S^E index and the net charges.

[1] Unpublished data.

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Comments on the USP XX Gas Chromatographic Analysis of Alcohol in Drugs and Drug Formulations

Keyphrases □ GC—USP XX GC analysis of alcohol in drugs and drug formulations □ Alcohol—USP XX GC analysis in drugs and drug formulations

To the Editor:

The analysis of the alcohol content in drug formulations is a part of not only elixir and tincture monographs but also is included as a limit test for residual alcohol from the synthesis of some drug substances.

The performance of a divinylbenzene polymer for the GC analysis of alcohol was described previously (1), and it was concluded that there were definite advantages with the use of porous polymer beads for the analysis of alcohol in pharmaceuticals. In 1975 the 12th edition of the "Official Methods of Analysis of the Association of Official Analytical Chemists" (2) adopted a GC method for the analysis of alcohol in drugs which was based on a collaborated method developed previously (3). This procedure utilized a flame ionization detector and a column packed with a 80–100 mesh copolymer of ethylvinylbenzene and divinylbenzene[1] (I) operated at 130° with a retention time of ~5 min for acetonitrile, the internal standard. The USP XX (4) changed the chromatographic procedure for alcohol to essentially that cited previously (3). The change of the column packing to I was an improvement in the USP method since it eliminated interferences caused by column bleed and the late elution of water experienced with the earlier polyethylene glycol column. Unfortunately, it now appears that a suitable grade of I is no longer commercially available.

Data to support this conclusion was developed during a recent evaluation of the alcohol analysis for dexamethasone elixir.[2] Six lots of I, including both the 80–100 and 100–120 mesh sizes, were evaluated to determine the extent of the problem. These lots represent commercially available materials between 1976 and 1981. Both coiled and U-shaped glass columns were packed and used with three different gas chromatographs[3]. Even though both the temperature and the nitrogen flow rate were adjusted, complete baseline separation of the alcohol and acetonitrile peaks was not achieved with any lot of Compound I. The alcohol peak also exhibited marked tailing, which was not present in the chromatograms published by Falcone (3) or those by Hollis (5) who did some of the first experimental work with porous polymer beads. The acetonitrile peak remained symmetrical regardless of packing pretreatment, column temperature, or whether injected alone or with alcohol. Tailing of the alcohol peak can be reduced by either the chloroform soxhlet extraction of I prior to packing the column or by raising the column temperature. The change in resolution can be attributed to the interaction of alcohol with residual polymerization compounds in I. Tailing and resolution factors calculated during this evaluation are listed in Table I.

During conditioning, current lots of I released vapors suggestive of the drying oils found in paints. This odor can also be detected in the bulk packing container, yet the remainder of a bulk lot which was received in 1968 is odorless. The difference in the odor itself indicates that there has been some change in the polymer synthesis which introduces different residual compounds. IR analysis of the oily residue extracted with chloroform showed that at least three compounds are vaporized during column conditioning. A brochure (6) distributed by the manufacturer of I states that "... any residual chemical in the bead can contribute to spreading of the peak, change in retention time, or loss of resolution." This brochure also recommends conditioning for at least 2 hr at 250°. All columns that were evaluated had been conditioned at 235° for 16 hr. One column that was conditioned for a second 16-hr period did not show any improvement in its performance. Only the 100–200 mesh lot, which was exhaustively extracted with chloroform, showed a reduction in the tailing of the alcohol peak. The observed experimental results substantiate the manufacturer's information about residual chemicals in the polymer beads, in that there has been a deterioration in peak resolution, and there is tailing for hydroxyl compounds which was not observed in the collaborative study (3). There is also great variation in column performance between different batches of I.

It is the opinion of this author that the data in Table I demonstrate that acetonitrile is no longer a suitable internal standard for the GC analysis of alcohol. Either the resolution factor or the alcohol tailing factor requirement of USP XX can be met but not both with the same set of chromatographic conditions and the 100–200 mesh size specified in the Alcohol Determination monograph. Of the lots tested, only one lot of 80–100 mesh met all the requirements, except for mesh size, of the system suitability test. A series of five replicate injections of the alcohol standard preparation onto this column had a relative standard deviation (*RSD*) of 2.98% for the peak height ratios, which is less than the 4.0% required by this system suitability test. The *RSD* for the peak area ratios from these same injections was 0.28%. The average result cal-

[1] Poropak Q, Waters Associates, Milford, Mass.
[2] Analyses were part of a study for the Food and Drug Administration's Compendial Monograph Evaluation and Development Program for Dexamethasone monographs in the USP XX.
[3] Hewlett-Packard, model 5830A; Schimadzu, model GC-MINI2; Nuclear-Chicago, model 4740.

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