# METHYL DERIVATIVES OF FURAN

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The reactivity and physicochemical properties of furan methyl derivatives $I-VIII$ have been calculated by the HMO and Del Re method. The theoretical data have been correlated with experimental reactivities as well as NMR spectra and experimental ionisation potentials of compounds $I-VIII$.

The present work relates to the reactivity and behaviour of the furan ring in dependence on substitution with methyl groups. By means of a simple HMO method there have been calculated indices of the chemical reactivity for all the positions of the furan nucleus with compounds $I-VIII$, namely, π-electron density (q), superdelocalisability (S_i), and free valence (F) values. The π-electron density values were then correlated with chemical shift values (δ) in NMR spectra. In view of scattered data, the Del Re method was used to calculate charge values for the particular positions of the furan nucleus with compounds $I-VIII$ on the basis of the σ-approximation and the total charge values of the σ- and π-approximation $(\xi^{\top})$ obtained by summing up, were then again correlated with shift values in NMR spectra. Furthermore, there were correlated the HOMO energy values obtained from HMO calculations, with ionisation potential data obtained by mass spectral measurements. Finally,
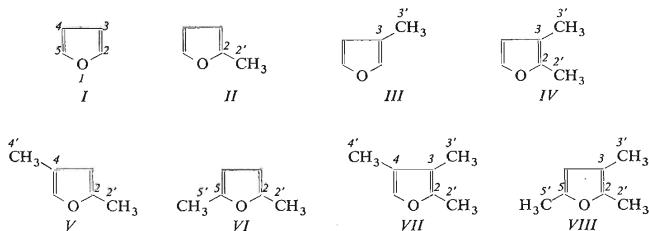
chemical reactivity indices were compared with data of the electrophilic, nuoleophilic, and radical substitution on the furan nucleus.
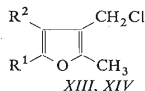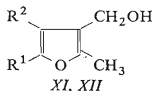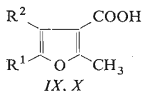
IX, XI, XIII; R^1 = H; R^2 = CH$_3$ *X, XII, XIV;* R^1 = CH$_3$; R^2 = H

By means of a simple HMO calculation, there have been obtained data of the π-electron densities, free valences, and superdelocalisabilities for the particular positions on the furan ring with compounds *I — VIII*. Coulombic and exchange integrals were approximated according to formulae

$$\alpha_X = \alpha_C + h_X\beta_{CC} \qquad \beta_{CX} = k_{CX}\beta_{CC} ,$$

wherein h_X and k_{CX} are empirical parameters according to Streitwieser[1] for $h_O = 2\cdot0$; $k_{CO} = 0\cdot8$. For the methyl group, a heteroatomic model was used with parameters $h_{CH_3} = 2\cdot0$ and $k_{C-CH_3} = 0\cdot27$. The other values are conventional, $\alpha_C = 0$ and $\beta_{CC} = 1\cdot0$. The thus-calculated reactivity indices are in better accordance with experimental data than those of an inductive and hyperconjugation model. The σ-charge calculations were performed by the method of Del Re[2] with the reported[3] parametrisation.

As the starting material in the preparation of 2,3,4-trimethylfuran (*VII*) and 2,3,5-trimethylfuran (*VIII*), there have been used 2,4-dimethyl-3-furoic acid[4] (*IX*) and 2,5-dimethyl-3-furoic acid[5], resp. These acids were reduced with sodium bis-(methoxyethoxy)aluminium hydride in ether[6] to alcohols *XI* and *XII*, resp. The attempted conversion of these alcohols to *p*-toluenesulfonates[7] or the attempted reduction of their complexes with pyridine–sulfur trioxide[8] failed. Consequently, the alcohols *XI* and *XII* were converted by the action of thionyl chloride in pyridine[9] to the chloromethyl derivatives *XIII* and *XIV* and the latter without isolation reduced with lithium aluminium hydride with the formation of the trimethyl derivatives *VII* and *VIII*.

EXPERIMENTAL

Temperature data are uncorrected.

The commercial (Fluka, Switzerland) furan (*I*) and 2-methylfuran (*II*) were dried and rectified, b.p. 31·5°C and b.p. 63°C, resp. 3-Methylfuran (*III*), 2,3-dimethylfuran (*IV*), 2,4-dimethylfuran (*V*), and 2,5-dimethylfuran (*VI*) were prepared by reported procedures[5,10−12] and their constants were in accordance with the literature[13].

2,4-Dimethyl-3-hydroxymethylfuran (*XI*) and 2,5-Dimethyl-3-hydroxymethylfuran (*XII*)

To a solution of 2,4-dimethyl-3-furoic acid (*IX*) or 2,5-dimethyl-3-furoic acid (*X*) (14 g each) in ether (200 ml) there was added with stirring at room temperature a 70% solution (55·7 ml; 0·2 mol) of sodium bis(2-methoxyethoxy)aluminium hydride. After 4 h, the reaction mixture was decomposed with dilute aqueous sulfuric acid, the ethereal layer washed with water and aqueous sodium carbonate, dried over anhydrous magnesium sulfate, and evaporated. Distillation of the residue afforded 7 g (56%) of the alcohol *XI*, b.p. 89°C/10 Torr, or 8·5 g (67%) of the alcohol *XII*, b.p. 91°C/10 Torr. For $C_7H_{10}O_2$ (126·2) calculated: 66·64% C, 7·99% H; found (*XI*): 66·35% C, 8·03% H; found (*XII*): 66·71% C, 8·12% H.

2,3,4-Trimethylfuran (*VII*) and 2,3,5-Trimethylfuran (*VIII*)

To a solution of the alcohol *XI* or *XII* (12·6 g each; 0·1 mol) in ether (40 ml) and pyridine (20 ml) there was added dropwise over 1 h at −10°C thionyl chloride (11·9 g; 0·1 mol) in ether (30 ml), the whole stirred at the same temperature for 1 h, and poured onto ice and water. The ethereal layer was washed with ice-cold water, dilute (1 : 10) hydrochloric acid, 3% aqueous sodium hydroxide, and water again, and dried with anhydrous potassium carbonate. The dry ethereal solution was added dropwise into a suspension of lithium aluminium hydride (3·8 g; 0·1 mol) in ether (100 ml), the whole stirred at room temperature for 24 h, and decomposed with dilute sulfuric acid. The ethereal layer was washed with aqueous sodium carbonate and water, dried over anhydrous calcium chloride, evaporated, and the residue distilled to afford 2·7 g (28%) of 2,3,4-trimethylfuran (*VII*), b.p. 51°C/55 Torr (reported[14], b.p. 54−55°C/57 Torr) or 2·5 g (23%) of 2,3,5-trimethylfuran (*VIII*), b.p. 57°C/55 Torr (reported[14], b.p. 51·5°C/62 Torr.)

TABLE I

Chemical Shifts (δ), π-Electron Densities (q), σ-Charges, and Total Charges (ξ^T) for the Particular Positions of Compounds *I*— *VIII*

Compound	Position	σ	q	ξ^T	δ
I	2	+0·047	−0·015	+0·032	445·4
	3	−0·041	−0·090	−0·131	382·1
II	3	−0·045	−0·146	−0·191	356·2
	4	−0·041	−0·086	−0·127	370·5
	5	+0·047	−0·054	−0·007	435·5
III	2	+0·044	−0·073	−0·029	430·9
	4	−0·044	−0·103	−0·147	343·0
	5	+0·047	−0·011	+0·036	438·2
IV	4	−0·044	−0·099	−0·143	368·3
	5	+0·046	−0·052	−0·006	431·3
V	3	−0·048	−0·159	−0·207	348·9
	5	+0·044	−0·113	−0·069	421·8
VI	3 = 4	−0·045	−0·144	−0·189	348·0
VII	5	+0·043	−0·109	−0·066	420·6
VIII	4	−0·048	−0·156	−0·204	343·0

NMR Spectra and Ionisation Potentials

The NMR spectra were measured on Varian XL-100-15 and Tesla BS-477 apparatus in Central Laboratories of the Prague Institute of Chemical Technology. The chemical shift values were extrapolated to zero dilution in deuteriochloroform and determined with the accuracy of 0·1 Hz. The ionisation potential values were measured by mass spectrometry[15] with the accuracy of ±0·1 eV. The ionisation potential of argon, IP = 15·75 eV, was used as standard. The π-electron density values, calculated on the basis of the π-approximation by the HMO method, were correlated with δ shifts in NMR spectra of compounds *I—VIII*. The σ, η, ξ^T, and δ values for the particular positions of the furan ring are shown in Table I (the δ values are expressed in Hz).

The HMO calculations were performed with the use of a standard program (author, Dr V. Kvasnička) on a NE 803B computer. Calculations by the method of Del Re were carried out on a Tesla 200 computer in the Computing Centre of the Prague Institute of Chemical Technology.

RESULTS AND DISCUSSION

It may be seen from Table I that the proton chemical shift values decrease with the increasing π-electron density in the same position of the furan ring. The correlation field of these values is divided into two groups. Fig. 1 shows this dependence for the α and β protons of the furan ring in particular (straight lines *c*). At both the positions, there is an obvious grouping of points into two straight lines (*a* and *b*). In the neighbourhood of line *b* there are situated those protons of the furan nucleus
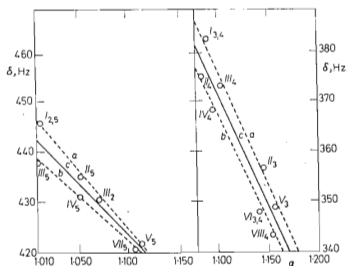

Fig. 1

Dependence of Proton Shifts in NMR Spectra on the π-Electron Density in the Corresponding Position of the Furan Ring

α-Protons, straight line *a*, $\delta = -242\cdot287q + 691\cdot170$, $r = 0\cdot9996$ (4 points); *b*, $\delta = -180\cdot102q + 620\cdot461$, $r = 0\cdot9995$ (3 points); *c*, $\delta = -219\cdot284q + 665\cdot036$, $r = 0\cdot9515$ (7 points). β-Protons, straight lines *a*, $\delta = -464\cdot432q + 887\cdot509$, $r = 0\cdot9960$ (4 points); *b*, $\delta = -450\cdot379q + 863\cdot438$, $r = 0\cdot9999$ (4 points); *c*, $\delta = -478\cdot791q + 899\cdot470$, $r = 0\cdot9562$ (8 points). Indices of compound numbers designate the position of the corresponding proton.

which lie in the "*meta*" position with respect to the methyl group. The other protons occur in the neighboorhood of straight lines *a*. All these correlations are considerably significant even in tests on 99·9% of significance.

In connection with the aim to smooth the scattering, there was attempted to include into the correlation also the σ-charge values, calculated by the Del Re method. It has been demonstrated[16] that data furnished by this simple method are in many cases comparable with those obtained by more complex and time-consuming methods such as EHT or CNDO. The values of thus-calculated σ charges as well as ξ^T total charges are shown in Table I. The result of the correlation of these values with chemical shifts is shown on Fig. 2. In the correlation of total charges, we may observe an equalisation of α and β positions while the groupings of protons in "*meta*" position to the methyl residue and of other protons remain untouched. This grouping is thus due to factors which are not covered in calculation methods. According to our experience, this effect does not occur with the analogous compounds of the thiophene series. It may be thus assumed that the diene character or the resemblance to an unsaturated ether play an important role in the furan series. The correlation of total charges with chemical shifts is again on the 99·9% significance level. The de-
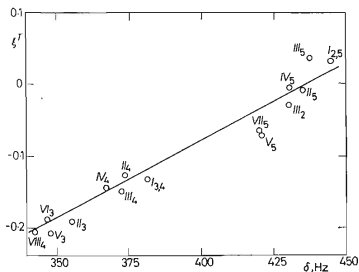

FIG. 2

Dependence of Total $\pi + \sigma$ Charges on Proton Shifts in NMR Spectra of Compounds *I—VIII*

TABLE II

HOMO Energies (k_1) and Ionisation Potentials (IP) of Compounds *I—VIII*

Compound	*I*	*II*	*III*	*IV*	*V*	*VI*	*VII*	*VIII*
k_1	0·618	0·507	0·566	0·445	0·470	0·405	0·425	0·357
IP, eV	9·65	9·10	9·15	8·90	9·05	8·90	9·00	8·50

pendence of the ξ^T total charge on the δ chemical shift is defined by the final relation

$$\xi^T = 0.00211\delta - 0.92398 \quad r = 0.96773 \text{ (for 15 points)}$$

The dependence between the ionisation potential IP values and the HOMO energy values (k_1) obtained from the HMO calculation with compounds $I - VIII$ is shown in Table II. Also this correlation is on the 99.9% significance level. The methodic error in the IP ionisation potential measurement is relatively high $(\pm 0.1$ eV$)$. The dependence of the ionisation potential on the HOMO energy values (k_1) is defined by the final relation

$$IP = 3.4403k_1 + 7.400 \quad r = 0.9241 \text{ (for 8 points)}$$

CHEMICAL REACTIVITY

Experimental data on the reactivity of the furan nucleus are rather numerous in the field of electrophilic substitution in contrast to the nucleophilic and radical substitution. Table III shows predictions on the reactivity in particular positions of the furan nucleus on the basis of calculated reactivity indices along with experimental reactivity orders. Prediction of the reactivity in particular positions of the furan nucleus in electrophilic substitutions on the basis of π-electron densities is at variance with experimental data. An almost absolute accordance with predictions may be observed in the case of superdelocalisability S_e values. The π-electron density values are in accord with the reactivity of the furan nucleus towards nucleophilic agents; the superdelocalisability S_n values are in an equally good agreement. In the evaluation of the radical reactivity of the furan nucleus, both the free valence values and the S_r superdelocalisabilities may be used with equal qualitative results. In the case of radical reactions, considerable discrepancies may be observed with the use of the N-bromosuccinimide radical initiated bromination as the testing reaction. The thus-obtained results are quite opposite to those concerning the reactivity in the radical methylation with diacetyl peroxide. The bromination with N-bromosuccinimide does not appear suitable for the radical reactivity assays[32] because of the somewhat obscure mechanism and an obvious involvement of the crystal lattice of the reagent. Similar discrepancies between the reactivity prediction and bromination results may also be observed in the thiophene series[30]. On the other hand, the radical methylation with diacetyl peroxide takes place in good agreement with the reactivity prediction on the basis of calculated data.

Conclusively, the S_e, S_n, and S_r superdelocalisability values are fairly more suitable for predictions of the reactivity in particular positions of the furan nucleus than the static indices.

TABLE III

Theoretical and Experimental Reactivity Data of Compounds I—VIII

Reaction type	Compound	Positional reactivity from tests			Reaction, literature
		q	S_i	Experiment	
S_E	I	3 > 2	2 > 3	2 > 3	acylation[17]
	II	3 > 4 > 5	2 > 3 > 4	5 > 3 > 4	acylation[18], protonation[19], alkylation[20], formylation[21]
	III	4 > 2 > 5	2 > 5 > 4	2 > 5 > 4	acylation[22], nitration[23], mercuration[24]
	IV	4 > 5	5 > 4	5 > 4	formylation[25]
	V	3 > 5	5 > 3	5 > 3	formylation[26]
	VI	3 = 4	3 = 4	3 = 4	acylation[17,27], nitration[23]
	VII	5	5	5	formylation[14], mercuration[27,28]
	VIII	4	4	4	acylation[18], mercuration[27]
S_N	I	2 > 3	2 > 3	2 > 3	H—D exchange (tert-butylpotassium)[2]
	II	5 > 4 > 3	5 > 4 > 3	5 > 4 > 3	
	III	5 > 2 > 4	5 > 2 > 4	5 > 2 > 4	
		F			
S_R	I	2 > 3	2 > 3	2 > 3	acylation[29], phenylation[30]
	II	5 > 3 > 4	5 > 3 > 4 > 2a	2a > other	bromination (N-bromosuccinimide)[31,32]
				5 > 3, 4	acetylation[29]
	III	2 > 5 > 4	2 > 5 > 4 > 3a	2, 5 > 4, 3a	bromination (N-bromosuccinimide)[33]
				2 > 5 > 4	acetylation[29]
	V	5 > 3	5 > 3	5 > 3	acetylation[29]
	VI	3 = 4	3 = 4 > 2a, 5a	3 = 4 > 2a, 5a	acetylation[29]
				2a, 5a > 3 = 4	bromination (N-bromosuccinimide)[34,35]

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