Regioselectivity and reactivity in the addition of trichloromethyl radicals to amides of unsaturated carboxylic acids

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The AM1 method was used to analyze the factors that correlate with regioselectivity in the addition of radicals to 1,2-disubstituted unsaturated compounds. The rate constants of the addition of $^{\bullet}CCl_3$ radicals to RCH=CHC(O)X (R = Ph, Me; X = N-pyrrolidyl) were determined by ESR. The analysis of the spin density distribution in mono- and 1,2-disubstituted alkenes and the experimental values for the rate constants of the addition of $^{\bullet}CCl_3$ radicals to these alkenes allowed the authors to conclude that the efficiency of the addition of $^{\bullet}CCl_3$ to unsaturated compounds depends only on steric effects.

Key words: regioselectivity, reactivity, addition reactions, AM1.

The determination of the most preferable positions for the addition of free radicals to unsaturated compounds and the estimation of their reactivity are important tasks from both theoretical and practical points of view since the processes of radical addition are used extensively and successfully in organometallic synthesis. In the present study, an attempt was made to analyze the factors influencing the regioselectivity and reactivity of the addition of $^{\bullet}CCl_3$ free radicals to disubstituted unsaturated molecules RCH=CHC(O)X (R = Ph (**1**), Me (**2**); X = *N*-pyrrolidyl) using quantum chemical and ESR methods.

The regioselectivity of radical addition to unsaturated fragments of molecules may be determined by a number of factors. It has been shown[1] that the addition of radicals to the unsaturated part of a molecule is controlled by the indices of the free valence of the corresponding π-centers. Within the limits of the frontier orbital approach it has been found[2] that depending on the degree of «philicity» of the attacking radical, a correlation of the regioselectivity of the addition with the squares of the HOMO or LUMO coefficients or with the sum of the squares of the HOMO and LUMO coefficients can be observed. In the latter case the radical is characterized as ambiphilic. The regioselectivity of the addition also depends on the stability of the intermediate radicals[3], that result from the addition of a $^{\bullet}CCl_3$ radical to the molecule RCH=CHC(O)X, since the $^{\bullet}CCl_3$ radical can add either to the α-carbon atom (Eq. 1) or to the β-carbon atom (Eq. 2):

$$\dot{C}Cl_3 + RCH{=}CHC(O)X \longrightarrow \underset{\mathbf{A}}{R\dot{C}HCH(CCl)_3C(O)X}, \quad (1)$$

$$\dot{C}Cl_3 + RCH{=}CHC(O)X \longrightarrow \underset{\mathbf{B}}{RCH(CCl)_3\dot{C}HC(O)X}. \quad (2)$$

In oder to evaluate the influence of electronic and energetic effects on the probability of reactions (1) and (2) we performed quantum chemical calculations of molecules **1** and **2** as well as of radical adducts **A** and **B**. We determined the structures and the heats of formation of the molecules $RCHClCH(CCl_3)C(O)X$ and $RCH(CCl_3)CHClC(O)X$ (R = Ph (**3**, **4**); R = Me (**5**, **6**)), which are the products of the addition of CCl_4 to molecules **1** and **2**. The choice of a C(O)Y type group as a substituent stems from the fact that in recent years mono- and disubstituted unsaturated compounds with such substituents (Y is a chiral and Y = X is an achiral substituent) are often used in the synthesis of chemical substances containing various carbon—element bonds.[3–6]

Results and Discussion

The calculations of molecules **1**—**6** and radicals $Ph^{\bullet}CHCH(CCl_3)C(O)X$ ($^{\bullet}R^1$), $PhCH(CCl_3)^{\bullet}CHC(O)X$ ($^{\bullet}R^2$), $Me^{\bullet}CHCH(CCl_3)C(O)X$ ($^{\bullet}R^3$) and $MeCH(CCl_3)^{\bullet}CHC(O)X$ ($^{\bullet}R^4$) were carried out by the AM1 method[8] with full optimization of geometry. The sums of the squares of the coefficients of the $2p_z$-AO in the frontier molecular orbitals (FMO) of the C(1) and C(2) carbon atoms (Scheme 1) in molecules **1** and **2** (*Z* axis is perpendicular to the HCCH plane) are given in Table 1.

It follows from these data that on the α-carbon atom of monomer **1** the total frontier π-electron density and the index of free valence are maximal. Thus radicals, regardless of their polar properties would preferentially attack the α-position (atom C(1)). At the same time free radicals would add to monomer **2** preferentially at the β-carbon atom C(2) to form $^{\bullet}R^4$ radicals.

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya*, No. 3, pp. 452—455, March, 1995.

1066-5285/95/4403-0437 $12.50

Table 1. Sums of the squares of the coefficients q^2 of $2p_z$-AO in FMO and indices of free valence (IFV) of C(1) and C(2) atoms in molecules **1**, **2**, **11**—**13**

Molecule	C(1)		C(2)	
	q^2	IFV	q^2	IFV
1	0.377	0.570	0.260	0.520
2	0.266	0.680	0.445	0.780
11	0.442	0.790	0.244	0.515
12	0.430	0.770	0.207	0.508
13	0.263	0.540	0.452	0.760

Table 2. Heats of formation ΔH_f (kcal/mol) of molecules **3**—**6** and radicals $\dot{R}^1$—$\dot{R}^4$ calculated by the AM1 method

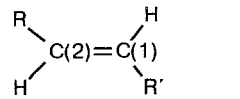
Molecule	ΔH_f	Radical	ΔH_f
3	−31.4	R^1	−4.5
4	−29.2	R^2	−2.3
5	−68.5	R^3	−44.3
6	−69.3	R^4	−41.3

The calculated heats of formation ΔH_f of molecules **3**—**6** and $^{\bullet}R^1$—$^{\bullet}R^4$ radicals are given in Table 2. It follows from this table that for the $^{\bullet}CCl_3$ radical addition to the α-carbon atom of molecule **1** is more profitable than addition to the β-carbon atom. In case of molecule **2** the heats of formation of compounds **5** and **6** differ insignificantly.

The calculated data given in Table 1 correlate with the experimental results on the regioselectivity of radical addition,[7] in particular for the addition of the $^{\bullet}CCl_3$ radical to molecule **1**. It has been shown[7] that the addition of CCl_4 and $CBrCl_3$ to **1** results in the formation of the compounds PhCHYCH(CCl_3)C(O)X (Y = Cl (**7**); Br (**8**)).

To verify the expediency of using similarly calculated data for the interpretation of the regiochemistry of the addition of free radicals to monomer **2** we experimentally investigated the addition of CCl_4 and $CBrCl_3$ to **2**. As a result of this reaction compounds MeCH(CCl_3)CHYC(O)X (Y = Cl (**9**), Br (**10**)) were synthesized in full accordance with the total distribution of electron density of the FMO and the indices of free valence of monomer **2**.

Scheme 1



1: R = Ph, R' = C(O)N

2: R = Me, R' = C(O)N

12: R = Ph, R' = H

13: R = H, R' = C(O)N

The interpretation of the regioselectivity of addition of free radicals to 1,2-disubstituted unsaturated monomers that was used in the present study is presumably of a general nature. In fact, from the calculation of the coefficients of the $2p_z$-AO in the FMO of PhCH=CHMe (**11**) (Table 1) it follows that radicals should add preferentially to the C(1) carbon atom (Scheme 1). These calculated results correlate fully with the values of the free valence indices (Table 1) and with the experimental data.[5,6]

The sums of the squares of the coefficients of the $2p_z$-AO in the FMO correspoding to carbon atoms C(1) and C(2) in PhCH=CH_2 (**12**) and CH_2=CHC(O)X (**13**) and the free valence indices for the same atoms are given in Table 1. It follows from these data that free radicals would preferentially add to the C(1) atom of molecule **12** and to the C(2) atom of molecule **13**. This is in agreement with numerous experimental results concerning the addition of various compounds to these molecules. Furthermore we point out that the squares of the coefficients of the AO in the FMO corresponding to carbon atoms C(1) and C(2) in molecule **12** are not substantially changed as a result of replacing the hydrogen atom at C(2) carbon atom with the C(O)X group. The replacement of the hydrogen atom at the C(2) atom in molecule **13** by a methyl group also results in minor changes in the squares of the coefficients of the AO of atoms C(1) and C(2) in the FMO.

In order to determine the reactivity of the $^{\bullet}CCl_3$ radical with respect to molecules **1** and **2** we determined the rate constants of the addition of $^{\bullet}CCl_3$ radicals to compounds **1** and **2** by ESR using the spin trapping technique.[9] $^{\bullet}CCl_3$ radicals were generated photochemically by the removal of a chlorine atom from CCl_4 by the $^{\bullet}Re(CO)_5$ radical.

$$\dot{Re}(CO)_5 + CCl_4 \longrightarrow ClRe(CO)_5 + \dot{C}Cl_3$$

$^{\bullet}Re(CO)_5$ radicals are formed as a result of destruction of $Re_2(CO)_{10}$ by irradiation with light at a wave length of $\lambda \approx 366$ nm.[10] During the photochemical interaction of CCl_4 with molecules **1** or **2** in the presence of $Re_2(CO)_{10}$ and nitrosodurene (ND; the latter was chosen as a spin trap for the identification of the intermediate free radicals) in a CH_2Cl_2 solution at room temperature the ESR spectra contained, in addition to the reported[11] signals of nitroxyls C, which are spin-adducts (SA) of $^{\bullet}CCl_3$ radicals with ND (a_N = 10.7, a_{Cl} = 1.3 Oe):

$$\dot{C}Cl_3 + N(O)Ar \xrightarrow{k_1} CCl_3N(\dot{O})Ar$$
C

(here Ar = 2,3,5,6-Me_4C_6H), we observed a doublet of

triplets from SA of R^1 radicals ND (a_N= 14.4 and $a_{\beta\text{-H}}$ = 6.9 Oe) or $^{\bullet}R^4$ with ND (a_N = 13.8 and $a_{\beta\text{-H}}$ = 8.6 Oe). In consequence of the different stabilities of the nitroxyls **C** and the SA of the $^{\bullet}R^1$ and $^{\bullet}R^4$ radicals with ND, the signals of nitroxyls $R^1N(^{\bullet}O)Ar$ or $R^4N(^{\bullet}O)Ar$ are distinctly visible in the ESR spectra 30 min after termination of the irradiation. The validity of the assignements made was confirmed by the coincidence of the values of the HFS constants for SA of $^{\bullet}R^1$ and $^{\bullet}R^4$ radicals with ND generated by an independent method, *viz.*, through the abstraction of a bromine atom from compounds $PhCHBrCH(CCl_3)C(O)X$ (**14**) and $MeCH(CCl_3)CHBrC(O)X$ (**15**) by $^{\bullet}Re(CO)_5$ radicals:

$$\mathbf{14} + \dot{R}e(CO)_5 \longrightarrow \dot{R}^1 + BrRe(CO)_5$$
$$\mathbf{15} + \dot{R}e(CO)_5 \longrightarrow \dot{R}^4 + BrRe(CO)_5$$

The rate constants of the addition (k_2) of $^{\bullet}CCl_3$ radicals to monomers **1** and **2** were determined by the known method[9] using the formula

$$\frac{dC^{abs}}{dC^{pres}} = 1 + \frac{k_2 C_M}{k_1 C_1},$$

where C_M is the concentration of monomer, C_1 is the concentration of ND, and C^{abs} and C^{pres} are the variations of the concentrations of SA of $^{\bullet}CCl_3$ radicals with ND at the linear region in the absence and in the presence of monomers **1** or **2** in the reaction mixture, respectively. It has been found through the least square approximation of the change of the signal intensity of nitroxyls **C** with the concentrations of monomer and ND that $k_2/k_1 = 5.49 \cdot 10^{-4}$ and $2.42 \cdot 10^{-4}$ for **1** and **2** respectively. On the assumption that the constant $k_1 = 9.1 \cdot 10^6$ L/(mol s)[9] the rate constants k_2 of the addition of $^{\bullet}CCl_3$ radicals to molecules **1** ($5.0 \cdot 10^3$ L/(mol s)) and **2** ($2.2 \cdot 10^3$ L/(mol s)) at 20°C were determined.

A comparison of the calculated rate constants of the addition of $^{\bullet}CCl_3$ radicals to molecules **1** and **2** with the respective rate constants of the addition of the same radicals to molecules **12** and **13** shows that the replacement of a hydrogen atom at the β-carbon atom in molecule **12** with a C(O)X group or the replacement of a hydrogen atom at the β–carbon atom in molecule **13** with a methyl group leads to a decrease in the rate constant of the addition of $^{\bullet}CCl_3$ radicals by a factor of 10^2 [12] or by a factor 10,[13] respectively. Thus, the decrease in the reactivity of $^{\bullet}CCl_3$ radicals on passing from monosubstituted monomers **12** and **13** to 1,2-disubstituted unsaturated compounds **1** and **2** is connected mainly with steric factors.

Experimental

ESR spectra of radicals were obtained on a «Radiopan SX-2547» spectrometer. Degassed reaction mixtures in glass ampules were irradiated in the resonator of the spectrometer using a DRSh-500 lamp. Glass filters were used to isolate the band with $\lambda \approx 366$ nm. ND concentration (monomer form) was varied in the range $3 \cdot 10^{-3}$—$4 \cdot 10^{-4}$ mol/L, and the monomers concentration varied from 2 to 0.2 mol/L. The change of the signal intensity of nitroxyl **C** over time was approximated by the linear least squares method. For all calculations the correlation coefficient was not less than 0.9.

The synthesis of compounds **7** and **8** has been described previously.[6] Using a similar procedure compounds **9** and **10** were obtained, *i.e.* CCl_4 and $BrCCl_3$ were added to monomer **2**. The structures of compounds **9** and **10** were determined by ^1H NMR (δ, ppm, $(CD_3)_2CO$): for **9** 5.13 (d, 1 H, OCHCl), 3.56 (octet 1:1:3:3:3:3:1:1, 1 H, $Cl_3CCH(CH_3)CHCl$, decoupling of the protons of the methyl group leads to the observation of a doublet), 1.6 (d, 3 H, CH_3), 3.66 (m, 2 H, CH_2), 3.4 (t, 1:2:1, 2 H, CH_2) and 1.95 (m, 4 H, CH_2CH_2); for **10** 5.1 (d, 1 H, C(O)CHBr), 3.44 (m, 1 H, Cl_3CCHCH_3), 1.69 (d, 3 H, CH_3), 3.68 (m, 2 H, CH_2), 3.4 (m, 2 H, CH_2) and 1.95 (m, 4 H, CH_2CH_2).

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Received August 30, 1994