Polar Effects in Radical Addition Reactions: Borderline Cases

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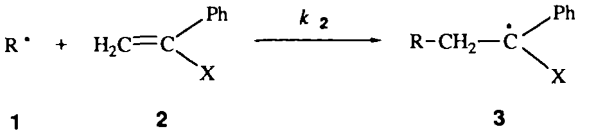
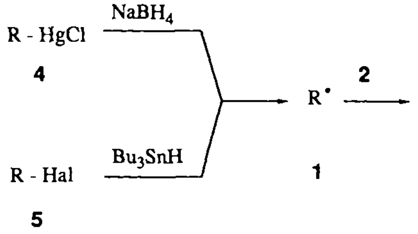
Methyl radicals substituted by one ester or nitrile group are on the borderline between nucleophilic and electrophilic behavior. In addition reactions of these borderline radicals to styrenes, polar effects of both, electron-withdrawing and electron-donating substituents at the alkene, increase the rates. But these polar effects are smaller compared to those of nucleophilic or electrophilic radicals. In consequence, the stability of the radicals formed during the addition of the borderline radicals to styrenes are of major importance for the rate of the reaction.

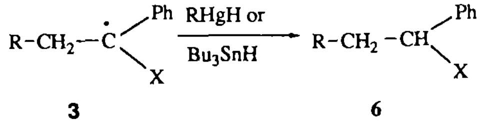
Rates and selectivities of radical reactions are often ruled by polar effects[1,2]. This is explained by the frontier molecular orbital (FMO) theory as an interplay between the SOMO of the radical and the LUMO or the HOMO of the reagent[2,3]. In nucleophilic radical reactions SOMO-LUMO interactions dominate, whereas electrophilic radical reactions are controlled by SOMO-HOMO interactions.

We have now studied the question how radicals behave, which are on the borderline between nucleophilic and electrophilic reactivity. As a model reaction the addition of radicals **1** to substituted styrenes **2**, which gives adduct radicals **3**, was used. Radicals **1** were generated by reduction of alkylmercuric chlorides **4** with $NaBH_4$ or by halogen abstraction from halides **5** with Bu_3SnH, and products **6** are formed by hydrogen abstraction (**3**→**6**)[3b].



	a	b	c	d	e	f	g
X	morpholino	OCH_3	CH_3	C_6H_5	$CO_2C_2H_5$	COC_6H_5	CN





$c\text{-}C_6H_{11}^\bullet$	$^\bullet CH(CO_2Et)_2$	$^\bullet CH_2CN$	$^\bullet CH_2CO_2Me$
7	**8**	**9**	**10**

In competition experiments of radicals with alkene pairs the influence of styrene substituents X on the rate of the radical addition was measured (Table 1)[4]. The data confirm the expected nucleophilicity of cyclohexyl radical **7**[2,5] and electrophilicity of malonyl radical **8**[6].

Table 1. Relative rates for the addition of radicals **7**–**10** to styrenes **2a**–**g**

2	Radical $\cdot C_6H_{11}$ (**7**)[a]	$\cdot CH(CO_2C_2H_5)_2$ (**8**)[b]	$\cdot CH_2CN$ (**9**)[b]	$\cdot CH_2CO_2CH_3$ (**10**)[b]
a		6.1[c]	3.6	4.5
b	0.08	2.1	1.0	0.9
c	≡1.0	≡1.0	≡1.0	≡1.0
d	3.6	1.2	1.6	
e	46	0.27	1.5	1.6
f	54	0.18	1.3	1.4
g	470			

[a] Radicals generated from cyclohexylmercury chloride, 20°C, mean error ±10%. – [b] Radicals generated from bromides with tributylstannane, 110°C, mean error ±10%. – [c] X = $N(C_2H_5)_2$.

Thus, the addition rate of cyclohexyl radical **7** becomes larger by a factor of 5900 at 20°C if substituent X is changed from an electron-releasing methoxy to an electron-withdrawing nitrile group, whereas the addition rate of malonyl radical **8** diminishes with

$$\underset{\mathbf{7}}{c\text{-}C_6H_{11}^\bullet} \xrightarrow[\text{H - Donor}]{\mathbf{2}} \underset{\mathbf{11}}{C_6H_{11}CH_2CHXPh}$$

$$\underset{\mathbf{8}}{^\bullet CH(CO_2Et)_2} \xrightarrow[\text{H - Donor}]{\mathbf{2}} \underset{\mathbf{12}}{(CO_2Et)_2CHCH_2CHXPh}$$

$$\underset{\mathbf{9}}{^\bullet CH_2CN} \xrightarrow[\text{H - Donor}]{\mathbf{2}} \underset{\mathbf{13}}{NCCH_2CH_2CHXPh}$$

$$\underset{\mathbf{10}}{^\bullet CH_2CO_2Me} \xrightarrow[\text{H - Donor}]{\mathbf{2}} \underset{\mathbf{14}}{MeO_2CCH_2CH_2CHXPh}$$

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increase of the electron-withdrwaing ability of the styrene substituent (NEt_2/COPh = 34, 110°C). A completely different substituent influence was observed with the cyanomethyl and methoxycarbonylmethyl radicals **9** and **10**, respectively. Now both, electron-donating morpholino and electron-withdrawing ester substituents, enhance slightly the rates (Table 1).

This behavior is similar to those cycloaddition reactions, in which both, SOMO-HOMO and SOMO-LUMO interactions, are of comparable relevance leading to U-shaped correlations between reactivities and polar substituent parameters[7]. Since in reactions of radicals **9** and **10** substituent effects on the addition rates are rather small (morpholine/methyl = 3.6 and 4.5; ester/methyl = 1.5 and 1.6), we have investigated the influence of the radical stabilizing ability of alkene substituents X on the addition rates. Alkenes **15** and **19** are suitable systems, because in alkene pairs **15**/**2d** and **19**/**2e** the polar substituent effects are of the same order[8], but in radical **16** the bridging methylene group between the two phenyl substituents inforces the overlap between the p electrons of the radical center and the phenyl groups. Therefore, adduct radical **16** is more stable than **3d** (X = Ph), in which the phenyl groups are twisted. Contrary to this, the radical destabilizing CF_3 group[9] in alkene **19** reduces the stability of **20** compared to adduct radical **3e** (X = $CO_2C_2H_5$).

The rate data show that the radical-stabilizing substituent increases the addition rate (k_{15}/k_{2d}) of cyanomethyl radical **9** by a factor of 10, and the destabilizing trifluoromethyl substituent decreases the rate (k_{19}/k_{2e}) by a factor of 14. This means that the stability effects are larger than the overall polar effects. With nucleophilic cyclohexyl radicals **7** the same stability effects change the rates only by factors of about 4. This is a relatively small influence compared to the large overall polar effect of 5900[10]. Radicals **9** and **10** are therefore borderline cases, in which the influence of polar substituents X in styrenes **2** on the SOMO-LUMO and SOMO-HOMO interactions for the most part compensate each other[11]. The U-shaped correlation between reactivities and polar substituent effects is shallow, and radical-stabilizing effects become very important[12].

Steric effects, which reduce the overlap between the radical center and the benzene ring in benzylic radicals **3**, should decrease the addition rate of radicals **9** and **10** more than that of the polar cyclohexyl radical **7**, where the stability of the benzylic radical plays only a minor role. This is confirmed by selectivity measurements with *tert*-butylstyrene **23** and methyl styrene **2c**. The *tert*-butyl substituent in **23** twists the phenyl ring out of the plane of the alkene by ca. 60°[13]. A similar steric effect should, therefore, destabilize benzyl radical **24** compared to **3c**. Actually, the addition rate of the cyanomethyl radical **9** is reduced by a factor of 14, whereas the nucleophilic cyclohexyl radical **6** is only slightly affected (k_{23}/k_{2c} = 0.64).

Conclusion: Cyanomethyl and methoxycarbonylmethyl radicals **9** and **10**, respectively, are on the borderline between nucleophilic and electrophilic behavior. As predicted by FMO theory, reactions of these radicals are slightly enhanced by electron-donating and by electron-withdrawing substituents. But the influence of polar substituent effects are so small that stability effects are of major importance.

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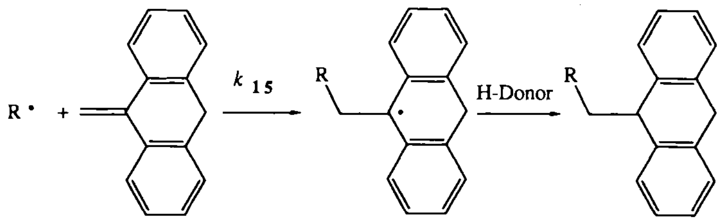
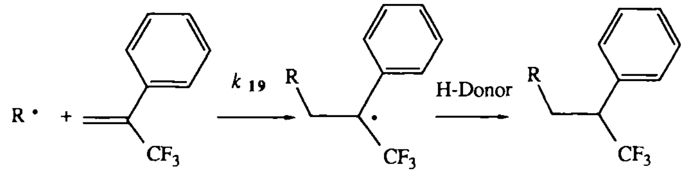


15 **16**

17 : R = CH_2CN
18 : R = C_6H_{11}

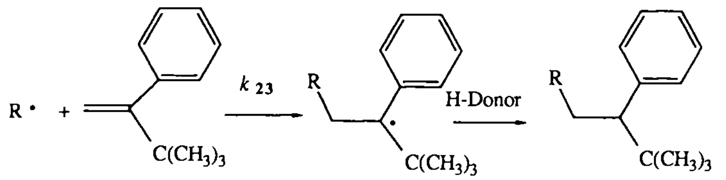
$R^•$	k_{15}/k_{2d}
• CH_2CN	10
• C_6H_{11}	3.9



19 **20**

21 : R = CH_2CN
22 : R = C_6H_{11}

$R^•$	k_{19}/k_{2e}
• CH_2CN	0.073
• C_6H_{11}	0.28



23 **24**

25 : R = CH_2CN
26 : R = C_6H_{11}

$R^•$	k_{23}/k_{2c}
• CH_2CN	0.07
• C_6H_{11}	0.64

Table 2. Yields, boiling points, ^{1}H-NMR data (δ[ppm] and J[Hz]), and analyses of new addition products

Compound	Yield %	b.p. (bath) [°C/Torr]	$-CH_2CHPhX$ $J(CH_2, CH)$	Formula (Molecular Mass)	Analysis			
						C	H	N
11b 2-Cyclohexyl-1-methoxy-1-phenylethane	12	100/0.5	4.18 (dd)	$C_{15}H_{22}O$	Calcd.	82.51	10.16	
			4.9, 8.5	(218.3)	Found	82.29	10.10	
11f 3-Cyclohexyl-1,2-diphenyl-1-propanone	49	74–75[a]	4.70 (t)	$C_{21}H_{24}O$	Calcd.	86.26	8.27	
			7.0	(292.4)	Found	86.30	8.35	
12f Ethyl-2-ethoxycarbonyl-5-oxo-4,5-diphenylpentanoate	43	200/0.02	4.75 (t)	$C_{22}H_{24}O_5$	Calcd.	368.1624		
			7.0	(368.2)	Found	368.1639 (MS)[b]		
13a 4-Morpholino-4-phenylbutanenitrile	43	160/0.2	3.42 (dd)	$C_{14}H_{18}N_2O$	Calcd.	73.01	7.88	12.16
			6.0, 7.5	(230.3)	Found	72.81	7.93	12.02
17 9-(Cyanoethyl)-9,10-dihydroanthracene	24	100–101[a]	3.90 (t)	$C_{17}H_{15}N$	Calcd.	87.55	6.44	6.00
			7.0	(233.3)	Found	87.55	6.36	5.95
18 9-(Cyclohexylmethyl)-9,10-dihydroanthracene	23		4.05 (t)	$C_{21}H_{24}$	Calcd.	276.1878		
			7.0	(276.4)	Found	276.1860 (MS)[b]		
21 4-Phenyl-5,5,5-trifluoropentanenitrile	27	100/0.4	3.46 (ddq)	$C_{11}H_{10}F_3N$	Calcd.	61.97	4.73	6.57
			4.0, 11.0, 18.0	(213.2)	Found	61.82	4.53	6.44
25 5,5-Dimethyl-4-phenylhexanenitrile	10	55/0.2	2.49 (dd)	$C_{14}H_{19}N$	Calcd.	83.53	9.51	6.96
			2.5, 12.5	(201.3)	Found	83.36	9.67	6.58
26 1-Cyclohexyl-3,3-dimethyl-2-phenylbutane	10	100/0.4	2.44 (dd)	$C_{18}H_{28}$	Calcd.	88.45	11.49	
			3.3, 12.0	(244.4)	Found	88.75	11.53	

[a] Melting point. — [b] Mass spectrum.

Experimental

NMR: Bruker WM 300 (TMS as internal standard). — MS: Finnigan MAT 311 A. — GC: Perkin-Elmer Sigma 3 with SE 30 (15%) and OV 11 (10%) columns.

Synthesis of addition products **11**–**14**, **17**, **18**, **21**, **22**, **25**, *and* **26**

Tin method: To a boiling solution of 3.0 mmol of halide **5** (cyclohexyl iodide, diethyl bromomalonate, bromoacetonitrile, methyl bromoacetate) and 3–30 mmol of alkene **2**, **15**, **19**, or **23** in 20 ml of toluene a solution of 1.05 mg (3.6 mmol) of tributylstannane and 60 mg (0.15 mmol) of dilauroyl peroxide or 25 mg (0.15 mmol) of AIBN in 2 ml of toluene was added within 10–60 min. After the reaction was completed, solvent and remaining alkene were distilled off, the residue was dissolved in 20 ml of ether, and stirred with 2–5 g of KF and 200–400 mg of dibenzo-18-crown-6 for 1–3 h. Filtration, distillation, and chromatography gave the addition products. Yields, analyses, and physical data of the new products are listed in Table 2.

Mercury method: To a solution of 600 mg (1.8 mmol) of cyclohexylmercury chloride and 2.0 g (9.6 mmol) of **2f** in 10 ml of methylene chloride 150 mg (3.8 mmol) of $NaBH_4$ in 1 ml of H_2O was added at 20°C. After 20 min the mixture was filtered and distilled. Chromatography gave 260 mg (49%) of product **11f**. Analysis and physical data are listed in Table 2.

Kinetic measurements[4]

Tin method: Ca. 0.20 mmol of halides **5** (diethyl bromomalonate, bromo acetonitrile, and methyl bromoacetate), 2.00 mmol of one alkene, and 2–30 mmol of a second alkene were dissolved in 5 ml of toluene and heated to 110°C. Under N_2 a solution of ca. 0.25 mmol of tributylstannane and ca. 0.05 mmol of dilauroyl peroxide in 1 ml of toluene was added. After 10 min the solution was cooled, concentrated, and the mixture of adducts was analyzed by GC.

Mercury method: To a solution of ca. 0.15–0.30 mmol of cyclohexylmercury chloride and a 10- to 50-fold excess of two alkenes in 10–30 ml of methylene chloride 0.3–1.5 mmol of $NaBH_4$ in 0.5–1.0 ml of H_2O was added at 20°C, and the mixture was stirred for 5–30 min. After filtration the mixture of the adducts was analyzed by GC.

CAS Registry Numbers

2a: 7196-01-2 / **2b**: 4747-13-1 / **2c**: 98-83-9 / **2d**: 530-48-3 / **2e**: 22286-82-4 / **2f**: 4452-11-3 / **2g**: 495-10-3 / **3a** (R = **8**, X = NEt_2): 116076-93-8 / **3a** (R = **9**): 116076-99-4 / **3a** (R = **10**): 116077-05-5 / **3b** (R = **7**): 116076-87-0 / **3b** (R = **8**): 116076-94-9 / **3b** (R = **9**): 116077-00-0 / **3b** (R = **10**): 116077-06-6 / **3c** (R = 7): 116076-88-1 / **3c** (R = **8**): 116076-95-0 / **3c** (R = **9**): 116077-01-1 / **3c** (R = **10**): 116077-07-7 / **3d** (R = **7**): 116076-89-2 / **3d** (R = **8**): 116076-96-1 / **3a** (R = **9**): 116077-02-2 / **3e** (R = **7**): 116076-90-5 / **3e** (R = **8**): 116076-97-2 / **3e** (R = **9**): 116077-03-3 / **3e** (R = **10**): 116077-08-8 / **3f** (R = **7**): 116076-91-6 / **3f** (R = **8**): 116076-98-3 / **3f** (R = **9**): 116077-04-4 / **3f** (R = **10**): 116077-09-9 / **3g** (R = **7**): 116076-92-7 / **7**: 3170-58-9 / **8**: 92303-29-2 / **9**: 2932-82-3 / **10**: 54668-31-4 / **11b**: 116076-78-9 / **11f**: 116076-79-0 / **12f**: 116076-80-3 / **13a**: 116076-81-4 / **15**: 40476-29-7 / **16** (R = CH_2CN): 116102-21-7 / **16** (R = cyclohexyl): 116102-22-8 / **17**: 116076-82-5 / **18**: 116076-83-6 / **19**: 384-64-5 / **20** (R = CH_2CN): 116077-10-2 / **20** (R = cyclohexyl): 116077-11-3 / **21**: 116076-84-7 / **23**: 5676-29-9 / **24** (R = CH_2CN): 116077-12-4 / **24** (R = cyclohexyl): 116077-13-5 / **25**: 116076-85-8 / **26**: 116076-86-9 / $BrCH_2(CO_2Et)_2$: 685-87-0 / $BrCH_2CN$: 590-17-0 / $BrCH_2CO_2Me$: 96-32-2 / $CH_2{=}CPhNEt_2$: 59590-86-2 / cyclohexyl iodide: 626-62-0 / cyclohexyl mercuric chloride: 24371-94-6

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[168/88]