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hydrocarbon with the same $\mathrm{IP_v}$. Monoolefin **6** shows $E^{\circ\prime} = 1.62$ V under the conditions of Table I and has an $\mathrm{IP_v}$ value of 7.84 eV.[14] Its $E^{\circ\prime}$ is 0.28 V lower than the predicted $E^{\circ\prime}$ from the aromatic hydrocarbon $\mathrm{IP_v}$ vs. $E^{\circ\prime}$ line. $E^{\circ\prime}$ is surprisingly insensitive to the bulk of alkyl groups near the formal charge-bearing atoms. Large structural changes, even in the atoms bearing the formal charge, have a very small effect on solvent stabilization differences for these two species with two-atom π systems and bulky alkyl groups. Although **2** and **6** show nearly identical oxidation behavior in an $\mathrm{IP_v}$ vs. $E^{\circ\prime}$ plot, they differ greatly from tetraalkylhydrazines, which also give two-atom π system cations. For example, tetramethylhydrazine has an $E^{\circ\prime}$ value 1.82 V below the line[15] and **4**, 1.41 V below the line.[16] As previously discussed in detail,[17] there is a large relaxation energy difference between the vertical and adiabatic cations from a hydrazine, caused by rehybridization from approximately sp^3 lone pairs in the neutral form to nearly pure p lone pairs in the adiabatic cation. A similar rehybridization obviously does not occur upon oxidation of peroxides. The electron being lost from a peroxide is from the antibonding combination of the pure p lone pairs. The two lone pairs on a divalent oxygen need to be considered as a pure p pair and a much more stabilized s rich pair,[18] and not (as organic chemists usually do currently[19]) as two sp^3 lone pairs.[20]

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[14] Mollère, P. D.; Houk, K. N.; Bomse, D. S.; Morton, T. H. *J. Am. Chem. Soc.* **1976**, *98*, 4732.

[15] $E^{\circ\prime}$ is 0.33 V, $\mathrm{IP_v}$ is 8.27 eV; Nelsen, S. F.; Kessel, C. R.; Brien, D. J. *J. Am. Chem. Soc.* **1980**, *102*, 702.

[16] $E^{\circ\prime}$ is 0.07 V, $\mathrm{IP_v}$ is 7.46 eV; Nelsen, S. F.; Hollinsed, W. C.; Grezzo, L. A.; Parmelee, W. P. *J. Am. Chem. Soc.* **1979**, *101*, 7347.

[17] (a) Nelsen, S. F. *Isr. J. Chem.* **1979**, *18*, 45. (b) Nelsen, S. F. *Acc. Chem. Res.* **1981**, *14*, 131.

[18] (a) Jorgenston, W. L.; Salem, L. "The Organic Chemist's Book of Orbitals"; Academic Press: New York, 1973; p 42. (b) Photoelectron spectroscopists have always done so, because $\mathrm{IP_v}$ for divalent oxygen clearly has a p orbital band shape (see ref 8).

[19] (a) Deslongchamps, P. "Stereoelectronic Effects in Organic Chemistry"; Pergamon Press: New York, 1983. (b) Kirby, A. J. "The Anomeric Effect and Related Stereoelectronic Effects at Oxygen"; Springer-Verlag: Berlin, 1983.

[20] We thank the National Science Foundation (Grant CHE-8026111), the Wisconsin Alumni Research Foundation, the Petroleum Research Fund, administered by the American Chemical Society, and the major instrument program of the National Science Foundation, as well as Amoco (for a Fellowship to D.L.K.) for financial support of this work.

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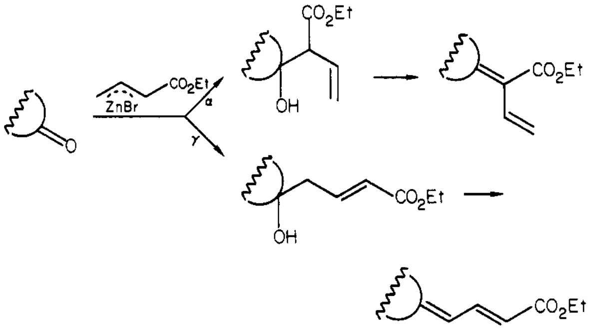
Regioselectivity in the Reformatsky Reaction of 4-Bromocrotonate. Role of the Catalyst and the Solvent in the Normal vs. Abnormal Modes of Addition to Carbonyl Substrates[†]

Summary: The regioselectivity of addition of the organozinc reagent derived from ethyl 4-bromocrotonate to 10 carbonyl substrates was found to be dependent on the polarity of solvents and the hardness of metal catalysts.

Sir: The Reformatsky reaction constitutes a mild and versatile method for the formation of carbon–carbon bonds.[1] Although most of the literature reports deal with the additions of α-bromoacetates to carbonyl compounds as means of a two-carbon homologation, several extensions of this reaction involving the halocarbonyl compounds as well as the electrophilic substrates are known.[1,2] Of these variations the reactions of unsaturated halo esters with carbonyl substrates particularly appealed to us since they provided a potential means of preparation of functionalized dienes required in our synthetic design of cyclopentanoid sesquiterpenes (eq 1).[3,4] The four-carbon homologation depicted in eq 1 is subject to expected regiochemical problems arising from the behavior of the delocalized reagents of this type.



(1)

In fact, only two reports described any attempts at regioselection, and both of these reports described experiments of limited scope.[5,6] Thus if a reliable method of regiodistinction for the additions of a crotonate unit to carbonyls existed, it would augment the compendium of synthetic methods dealing with reactions of delocalized species with electrophiles[7] where the problem of regiochemistry has not been adequately solved for various nucleophilic species derived from crotonate.

Further careful inspection of literature data also revealed that the normal or γ-mode of addition predominated in modest yields in all of the relatively few cases studied.[1] We suspected that these low yields reflected the outcome of the product isolation rather than the true profiles of the reactions since we have shown that the adducts of ethyl 4-bromocrotonate with various cyclopentanones were unstable under the conditions of their purification (distillation, chromatography, acid or base treatment).[3,4,8] In most instances, however, such purification is unnecessary since the free hydroxyls are usually immediately acetylated

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[1] Reviews: (a) Rathke, M. W. *Org. React* **1975**, *22*, 423. (b) Gaudemar, M. *Organomet. Chem. Rev. A* **1972**, *8*, 183.

[2] Variations of the Reformatsky reaction not included in the reviews above: (a) Orsini, F.; Pelizzoni, F. *Synth. Commun.* **1983**, *13*, 523 (alkylation with halides). (b) Stamm, H.; Steudle, H. *Tetrahedron* **1979**, *35*, 647 (additions to nitrones). (c) Kryczka, B.; Laurent, A.; Marquet, B. *Tetrahedron* **1978**, *34*, 3291 (additions to azirines). (d) Furukawa, M.; Okawara, T.; Noguchi, Y.; Terawaki, Y. *Chem. Pharm. Bull. Jpn.* **1978**, *26*, 260. Bellassoued, M.; Arous-Chtara, R.; Gaudemar, M. *J. Organomet. Chem.* **1982**, *231*, 185 (additions to imines). (e) Fauvarque, J. F.; Jutand, A. *Ibid.* **1977**, *132*, C17; **1979**, *177*, 273 (arylations); **1981**, *209*, 109 (vinylations). (f) Lucas, M.; Guette, J. P. *Tetrahedron* **1978**, *34*, 1685 (assymetric induction. (g) Mladenova, M.; Blagoev, B.; Kurtev, B. *Bull. Soc. Chim. Fr.* **1979**, II-78 (use of α-bromo amides).

[3] Short, R. P.; Hudlicky, T. *J. Org. Chem.* **1982**, *47*, 1522.

[4] Short, R. P.; Ranu, B. C.; Revol, J. M.; Hudlicky, T. *J. Org. Chem.* **1983**, *48*, 4453.

[5] Dreiding, A. S.; Pratt, R. J. *J. Am. Chem. Soc.* **1953**, *75*, 3717.

[6] Bellasoued, M.; Dardoize, F.; Frangin, Y.; Gaudemar, M. *J. Organomet. Chem.* **1981**, *219*, C1.

[7] For studies on the regioselection of crotonate-type nucleophiles, see for example: (a) Pffefer, P. E.; Silbert, L. S.; Kinsel, E. *Tetrahedron Lett.* **1973**, 1163. (b) Yoshimoto, M.; Ishida, N.; Hiraoka, T. *Ibid.* **1973**, 39. (c) Ahlbrecht, H.; Vonderheit, C. *Synthesis* **1975**, 512, (d) Evans, D. A.; Andrews, G. C.; Buckwalter, B. *J. Am. Chem. Soc.* **1974**, *86*, 5560.

[8] Hudlicky, T.; Koszyk, F. J., unpublished observations.

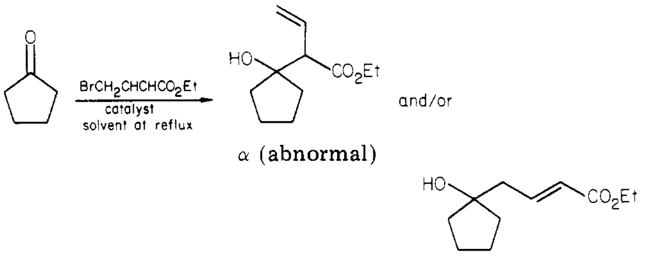
0022-3263/84/1949-1845$01.50/0

prior to their elimination to *dienes*. In some cases (entries **9a** and **9b**) the α-adducts form lactones that are stable. In general the reactions are quantitative and the crude reaction mixtures containing 90–95% of the product are easily analyzed by IR and ^1H or ^{13}C NMR spectroscopy or converted to acetates that are stable to purification. Indeed we have shown that the regioselectivity of these additions depended on the catalyst and the solvent used and that the composition of the crude reaction mixtures did not reflect the composition of isolated products. The instability of especially the abnormal or α-adducts may therefore have been the contributing factor to the belief that the Reformatsky reaction of unsaturated haloesters proceeds chiefly in the γ-mode.[1,2,5,6,9] Repetition of some of the literature cases confirmed this supposition. For example, furfural yielded mainly the α-adduct in benzene/Et_2O, although the literature informed us that γ-adduct should be the main product.[9] This mixture upon distillation decomposed to ethyl crotonate, furfural, dienic esters, and an enhanced amount of the γ-adduct. Thus in the original experiment the α-adduct partially (or totally) decomposed, leading the investigators to conclude that γ-addition predominated.[9] This supposition is in part supported by low *actual* yields of γ-products and in part by the scrambling observed when either a pure α-product or a mixture of α/γ adducts were heated to their boiling points under reduced pressure. These results also cast doubt on the assumed irreversibility of the Reformatsky reaction of unsaturated halo esters. Since only a few superficial studies of either the regioselectivity or the mechanism and the potential reversibility were available,[1b,5,6] we decided to undertake this investigation using several carbonyl substrates.

Since the carbon–carbon bond forming reactions involving *cyclopentanones* constitute a pivotal point of our research, we investigated these additions in greater detail. Tables I and II summarize the results of these experiments.

The conditions of the preparation of Zn/Cu catalyst leave an undetermined amount of acetic acid adsorbed on the surface.[10] Even though the copper content (determined by differential pulse polarography of the catalyst dissolved in HNO_3) was found to be only 0.225%, the presence of a small percentage of copper in the couple and the traces of acetic acid render the medium locally polar even in benzene or cyclohexane. Similarly, the dependence of regiochemistry of these additions on the softness/hardness of the medium is illustrated in Table II. As the softness of the secondary metal associated with zinc increases, the tendency for γ-addition also increases in a given solvent. This same tendency increases also with decreasing polarity of the solvent used with a given couple. Thus rigorously dried Zn/Cu couple does not give the same ratio of α/γ adducts as one freshly prepared from acetic acid and rinsed with anhydrous ether prior to use.[11] Addition of acetic acid to *anhydrous* catalysts or addition of HCl to anhydrous zinc produced results identical with those obtained while using Zn/Cu catalyst containing HOAc or zinc "activated" by washing with dilute HCl. The only deviation from the two-dimensional polarity–softness dependence occurred with THF and DME as solvents, where the apparent coordinating power of the solvents may have led to aggregates of the organozinc reagent, which may be bulky enough to permit only γ-addition.

Table I. Additions to Cyclopentanone



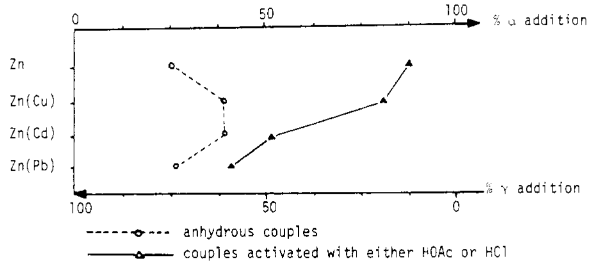
α (abnormal)

γ (normal)

solvent	catalyst (products α/γ))			
	Zn-(act. HCl)	ZnCu-(HOAc)	ZnCu-(dry)	Zn-(dry)
ethyl ether	100:0[a,c]	100:0	92:8	94:6
benzene	87:13	83:17	40:60	25:75
cyclohexane	70:30	66:34	22:78	29:71
tetrahydrofuran			0:100[b]	0:100[b]

[a] Ratio of α/γ estimated by ^1H NMR. [b] Not readily reproducible. [c] In all cases actual yields are in the range of 90–95%; *isolated* yields of the corresponding acetates that are stable to chromatography were 75–80%.

Scheme I. Regioselectivity Comparison for Various Couples in Benzene



The comparative results for the three metals studied are shown in Table II. At the extreme of this study, namely, with the usage of dry Zn–Pb catalyst in benzene, the rate of the Reformatsky reaction is retarded and a competition with the metal-induced coupling of the halo ester begins. The metal content of all catalysts was established by the use of differential pulse polarography and double-checked by atomic absorption spectroscopy. The relative contents are shown in Table III.

Following the completion of the study with cyclopentanone, we applied the two most selective conditions to a variety of substrates. These results are shown in Table IV. Thus exclusive α-addition can be obtained in ether by using Zn-Cu catalyst and traces of acetic acid while γ-addition predominates with anhydrous zinc in cyclohexane or tetrahydrofuran. It can be seen from Scheme I and Table I that even in benzene the regioselectivity can be reversed from predominantly γ-addition to chiefly α-addition by "activating" Zn or Zn(Cu) catalyst with trace amounts of acids. Thus it appears that the polarity of the medium and not the actual temperature of the reaction

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(9) English, J.; Gregory, J. D. *J. Am. Chem. Soc.* **1947**, *69*, 2123.

(10) Santaniello, E.; Manzocchi, A. *Synthesis* **1978**, 698. LeGoff, E. *J. Org. Chem.* **1964**, *29*, 2048.

(11) Prepared according to ref 10. The difference in regiochemical outcome between "wet" and "dry" catalyst is more prevalent in less polar solvents (see Table I). All couples have been prepared by stirring a solution of the requisite metal acetate in HOAc with zinc dust, decanting the excess acetic acid, and rinsing thoroughly with ether. The "wet" couples were used at this stage. The "dry" catalysts were obtained by an overnight drying in vacuo (~110 °C). All dry couples were pulverized prior to use.

(12) The structure of products was established by ^1H NMR, ^{13}C NMR, IR, and mass spectroscopy. The crude products were sufficiently pure to allow their immediate conversion to acetates. Without any attempts at purification, the adducts containing free hydroxyls decomposed on standing over periods of several days to several weeks.

Table II

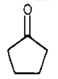
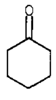
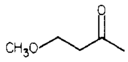
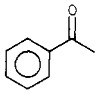
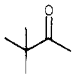
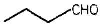
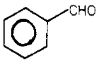
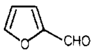
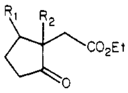
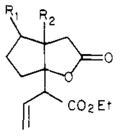
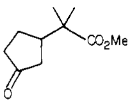
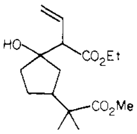
solvent	ZnCu(HOAc)	ZnCu(dry)	ZnCd(HOAc)	ZnCd(dry)	ZnPb(HOAc)	ZnPb(dry)
ethyl ether	100:0[a]	92:8	86:14	95:5	97:3	96:4
benzene	83:17	40:60	51:49	42:58	43:57	26:74

[a] Ratio of α/γ estimated by ^1H NMR.

Table III

ZnM couple	% comp of M by wt	% comp of M (mole)
ZnCu	0.6–0.7	0.62–0.72
ZnCd	2.5–3.0	1.5–1.7
ZnPb	4.0–6.0	1.3–1.8

Table IV

carbonyl substrate	conditions[g]	products $(\alpha/\gamma)^{a,b}$
 **1**	ZnCu(HOAc), Et_2O	100:0
	Zn(dry), THF	0:100[f]
	Zn(dry), cyclohexane	22:78
 **2**	ZnCu(HOAc), Et_2O	86:14
	Zn(dry), benzene	25:75
 **3**	ZnCu(HOAc), Et_2O	100:0
	Zn(dry), benzene	22:78
 **4**	ZnCu(HOAc), Et_2O	100:0
	Zn(dry), cyclohexane	10:90
 **5**	ZnCu(HOAc), Et_2O	100:0
	Zn(dry), cyclohexane	19:81
 **6**	ZnCu(HOAc), Et_2O	74:26
	Zn(dry), benzene	30:10, 0:100[f]
	Zn(dry), THF	0:100
 **7**	ZnCu(HOAc), Et_2O	86:14
	Zn(dry), THF	0:100
 **8**	ZnCu(HOAc), Et_2O	82:18
	Zn(HCl), benzene/Et_2O	77:23
	Zn(dry), benzene	
 **9**	ZnCu(HOAc), Et_2O	 **9a**, $R_1 = CH_3$; $R_2 = H$[c] 100% **9b**, $R_1 = H$; $R_2 = CH_3$[c] 80%
 **10**	ZnCu(HOAc), Et_2O	 100%[e]

[a] All yields were in the range of 90–95% (see ref 12). [b] Ratios of α/γ were estimated by integration in ^1H NMR spectra. [c] Reference 3. [d] Reference 4. [e] Reference 8. [f] Not readily reproducible. [g] All reactions carried out at reflux for a period of 2 h except for **9b** (slow addition, 12 h).[4]

plays the determining role in the regiochemical outcome. The repetition of three literature cases confirmed our suspicion that the isolation techniques altered the content of regioisomers.[5,6,9]

No attempts were made at this stage of the project to determine either the erythro/threo composition of the α-adducts or the E/Z composition of the γ-adducts although from the ^1H NMR spectra of the γ-adducts it seems that the integrity of E configuration in the crotonate unit has been preserved. The precise answers to the stereochemical questions will have to await the outcome of a more detailed study.

In all cases the hydroxy adducts decompose to crotonate and the starting carbonyl substrates on heating, chromatography on silica, or treatment with acids and bases. Although the mechanism of this decomposition may resemble a retro-ene reaction, these observations would lend some support to the original hypothesis of reversibility of this reaction.[1b] The detailed study of the actual mechanism and any potential reversibility of this reaction at the stage of metal alkoxides as well as further applications of this newly established regioselectivity in organic synthesis is the subject of current endeavor in our laboratories.

Typical Experimental Conditions. Catalyst. Finely divided zinc (pulverized either mechanically or by using an ultrasonic cleaner) was added to the solution of appropriate metal acetate in acetic acid. The plated couple was then rinsed with the solvent used in the reaction (for "acidic" or "activated" conditions it was used immediately) or dried at 100–110 °C (0.1 mmHg) for 12 h (for "anhydrous" conditions). Reagent Zn was not activated with dilute HCl rinse unless this was desired for the experiment. Zn dust was "dried" at 100–110 °C (0.1 mmHg) prior to use in either the reactions of the preparation of couples.

Reagents and Solvents. All solvents were dried with benzophenone/K (Et_2O, THF, cyclohexane, DME) or P_2O_5 (benzene). All reagents were freshly distilled.

The appropriate metal catalyst (2–4-fold excess by weight) was covered with 2–5 mL of the solvent of choice, and a crystal of iodine was added. A mixture of carbonyl substrate (0.001 mol) and 4-bromocrotonate (0.001 mol) was dissolved in 2 mL of the same solvent, and a few drops of this mixture added to the stirred suspension of catalyst under inert atmosphere. After 5–20 min at room temperature the reaction set in as evident by the disappearance of iodine coloring and/or onset of gentle reflux. The reaction mixture was then heated to reflux, the rest of the reagent mixture added over 30 min, and the reflux continued for 1 h, whereupon the reaction was cooled, diluted with ether, washed with cold NH_4Cl solution, and dried (Na_2SO_4). Evaporation gave a quantitative yield of oil that contained <5% of bromocrotonate, <5% of crotonate, and 90–95% of the appropriate product. The ratios of α- and γ-adducts were estimated from the signals of either the allylic methylene (2.2 ppm, doublet, 2 H; γ-adducts) or the α-methine (3.4 ppm, doublet, 1 H; α-adducts).

In some cases the crude reaction mixture was immediately dissolved in acetic anhydride (10 mL) containing triethylamine (0.001 mol) and 4-(dimethylamino)pyridine (5 mg). This mixture was stirred overnight, diluted with H_2O and ether, and washed with 5% NaOH. Drying and evaporation gave oily acetates, which were chromatographed for identification and confirmation of NMR yields estimates.

Acknowledgment. We thank the National Institutes of Health (AI-19749) for the support of this work.

[†] Dedicated to Prof. Milos Hudlicky on the occassion of his 65th birthday and in recognition of his contributions to organic fluorine chemistry.

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Additions and Corrections

Vol. 49, 1984

John A. Hyatt* and Peter W. Raynolds. Acyl Fluoride Friedel–Crafts Reactions. Regioselective Synthesis of 3-Acylacenaphthenes and 2-Acyl-6-alkylnaphthalenes.

Page 385. A final footnote should read: (9) For pertinent discussions of selectivity in Friedel–Crafts reactions, see: Gore, P. H. *Chem. Ind. (London)* **1974**, 727. Gore, P. H.; Siddiquei, A.; Thornburn, S. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1781. Gore, P. H.; Miri, A.; Rinaudo, J.; Bonnier, J.-M. *Bull. Soc. Chim. Fr.* **1978**, II-104.

Robert T. Hrubiec and Michael B. Smith*. Homoallylic Substitution Reactions of 1-Cyclopropyl-1-haloethane: Reaction with Lithium Dialkylcuprates.

Page 386. Column 1: structure **4** should be *trans*-2-nonene (not octene). Column 2: structure **8** should be $RCH_2CH_2CH{=}CH-$ (not $RCH_2CH{=}CH-$).