Communications

Correlation of the Reactivity of Ketones Relative to Different Nucleophiles

Summary: For a series of 26 ketones, the nucleophilic reactivity with various nucleophiles (BH_4^-, CN^-, SO_3^{2-}, NH_2OH, RS^-) reveals a linear correlation of the type $\log k/k_0 = B$ where k is the rate constant for a ketone and k_0 that for cyclohexanone; reverse reactions, i.e., carbinolamine decomposition, chromic acid oxidation, and decomposition of bisulfite addition compounds, show the same type of relationship.

Sir: Recent studies have demonstrated that it is possible to rationalize kinetic results of various reactions in terms of strain energies of reactants and products.[1,2] It appeared to us that such a method could be applied to the kinetic data obtained from nucleophilic additions to carbonyl compounds. In this communication, the reactivities of a number of ketones are compared to the reactivity of cyclohexanone (k_0) with respect to various nucleophiles (BH_4^-, CN^-, SO_3^{2-}, NH_2OH, RS^-). Cyclohexanone was chosen as reference since it is an essentially strain-free molecule on a conformational basis (Table I).

Table I. Rate Constants for Cyclohexanone with Respect to Various Nucleophiles

	k_0	solvent	ref
NH_2OH	0.9×10^4 L mol^{-1} s^{-1}	H_2O	6
SO_3^{2-}	0.7 L mol^{-1} s^{-1}	H_2O	7
CN^-	7.9×10^{-3} L mol^{-1} s^{-1}	H_2O/CH_3OH (50:50)	3
BH_4^-	0.17 L mol^{-1} s^{-1}	H_2O/dioxane (50:50)	3, 4
	5.7×10^{-2} L mol^{-1} s^{-1}	2-propanol	8
$HOC_2H_4S^-$	6.6×10^{-3} L^{-2} mol^{-2} s^{-1}	H_2O/EtOH (50:50)	9

The data from 26 ketones, whose reactivity varies from 10^{-9} to 10^4 (extreme values are 5×10^{-9} L mol^{-1} s^{-1} for the addition of CN^- to bicyclo[3.3.1]nonan-3-one and 1.9×10^4 L mol^{-1} s^{-1} for the addition of NH_2OH to bicyclo[3.2.1]octan-8-one),[3] are best interpreted by a linear relationship of the type $\log k = A \log k_0 + B$, where k is the rate constant for the ketone in question and k_0 that for cyclohexanone toward a given nucleophile.

Values of A and B are recorded in Table II.

The slopes of the straight lines, with few exceptions, are very close to one and thus, to a first approximation, the relationship can be simplified to $\log k/k_0 = B$. This result is analogous to that found by Ritchie[14] for variation of nucleophilic reactivity toward a given electrophile. In fact, if the ratio of the reactivity of two different nucleophiles toward any electrophile is constant, the reactivity of various electrophiles toward a given nucleophile will also be independent of the identity of the nucleophile. On the other hand, this relationship characterizes a reaction in which the attack of the nucleophile is rate determining as shown by Ritchie, in close collaboration with Jencks, by calculations for esters.[15]

It is important to note that this correlation includes results from both reactions with product-like and reactant-like transition states.[4,5,9,16,17] Although there are differences in selectivity of reagents due to the nature of the transition state,[16] the wide range (10^{13}) of values of the rate constants and the use of a logarithmic scale minimizes these differences,

Table II

	ketones	slope A	intercept B	corr coeff	no. of points
1	bicyclo[3.2.1]octan-8-one	0.85	0.45	0.999	3[a]
2	cyclobutanone	1.02	0.09		2[b]
3	4-*tert*-butylcyclohexanone	1.01	−0.008	0.999	5[c]
4	3-methylcyclohexanone	0.99	−0.05		2[d]
5	4-methylcyclohexanone	1.01	−0.08	0.999	3[e]
6	adamantanone	0.97	−0.46	0.997	5[f]
7	2-methylcyclohexanone	1.06	−0.48	0.999	3[g]
8	bicyclo[3.3.1]nonan-9-one	0.92	−0.72	0.995	4[h]
9	cycloheptanone	0.95	−0.95	0.999	3[e]
10	cyclopentanone	0.97	−1.18	0.991	6[i]
11	acetone	1.10	−1.19	0.981	6[j]
12	3,3,5-trimethylcyclohexanone	1.02	−1.33	0.992	4[o]
13	3,3,5,5-tetramethyl-4-acetylcyclohexanone	1.03	−1.36	0.952	3[k]
14	2-butanone	1.14	−1.45	0.991	4[l]
15	bicyclo[2.2.1]heptan-2-one	0.99	−1.48	0.994	6[i]
16	bicyclo[2.2.2]octan-2-one	0.97	−1.62	0.984	6[i]
17	bicyclo[3.1.0]hexan-3-one	0.97	−1.77	0.992	4[m]
18	tricyclo[5.2.1.0^{3,8}]decan-5-one	0.86	−1.80	0.956	3[k]
19	*trans*-3,5-di-*tert*-butylcyclohexanone	1.07	−1.85	0.996	3[k]
20	3,3,5,5-tetramethylcyclohexanone	1.05	−1.92	0.964	4[o]
21	1-methylbicyclo[2.2.1]heptan-2-one	0.91	−1.93	0.999	3[k]
22	4-twistanone (tricyclo[4.4.0.0^{3,8}]decan-4-one)	0.99	−1.96	0.989	4[n]
23	tricyclo[5.3.1.0^{3,8}]undecan-5-one	0.93	−2.28	0.970	3[k]
24	bicyclo[3.2.1]octan-3-one	0.83	−2.86	0.999	3[a]
25	bicyclo[3.2.1]6-octen-3-one	0.97	−3.79	0.998	3[a]
26	bicyclo[3.3.1]nonan-3-one	1.02	−5.77	0.994	3[a]

[a] NH_2OH,[3] CN^-,[3] BH_4^-.[3] [b] NH_2OH,[10] SO_3^{2-}.[7] [c] NH_2OH,[6] CN^-,[3] BH_4^-,[3] SO_3^{2-},[5] RS^-.[9] [d] NH_2OH,[6] RS^-.[9] [e] NH_2OH,[6] SO_3^{2-},[7] RS^-.[9] [f] NH_2OH,[6] SO_3^{2-},[7] CN^-,[3] BH_4^-,[3] RS^-.[9] [g] NH_2OH,[6] BH_4^-,[8] RS^-.[9] [h] NH_2OH,[3] CN^-,[3] BH_4^-,[3] RS^-.[9] [i] NH_2OH,[6] SO_3^{2-},[7] CN^-,[3] BH_4^-,[3] BH_4^-,[8] RS^-.[9] [j] NH_2OH,[6] SO_3^{2-},[7] CN^-,[11] BH_4^-,[12] BH_4^-,[8] RS^-.[9] [k] NH_2OH^-,[13] SO_3^{2-},[13] BH_4^-.[13] [l] NH_2OH,[6] SO_3^{2-},[7] CN^-,[11] BH_4^-.[12] [m] NH_2OH,[3] SO_3^{2-},[7] CN^-,[3] BH_4^-.[3] [n] NH_2OH,[3] SO_3^{2-},[7] CN^-,[3] BH_4^-.[3] [o] NH_2OH,[6] CN^-,[3] BH_4^-,[3] RS^-.[9]

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Table III. Rate Constants for Cyclohexyl Compounds in the Reverse Type Reactions

	k_0	solvent	ref
NH_2OH in basic conditions[a]	8×10^6 L mol^{-1} s^{-1}	H_2O	10
chromic acid oxidation[b]	3.5×10^{-3} L mol^{-1} s^{-1}	H_2O	19
decomposition of bisulfite addition compounds[c]	4.3×10^{-4} s^{-1}	H_2O	7

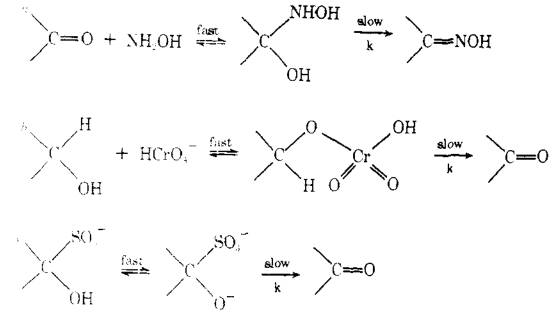

Table IV

ketones	slope A	intercept B	corr coeff	no. of points
cyclobutanone	0.80	−0.151	0.999	3[a]
cyclopentanone	1.06	0.165	0.999	3[a]
cycloheptanone	1.01	0.885	0.999	3[a]
cyclooctanone	1.00	1.157	0.998	3[a]
cyclononanone	1.00	0.40		2[b]

[a] NH_2OH in basic conditions,[10] chromic acid oxidation,[19] decomposition of bisulfite addition compounds.[7] [b] NH_2OH in basic conditions,[10] chromic acid oxidation.[19]

giving thus an apparent linear correlation.

Nevertheless, to a first approximation, $\log k/k_0 = B$ might be considered as a characteristic of the ketone and thus a function of the difference in internal energy between the ketone studied and cyclohexanone. However, if we plot B vs. f (ketone strain energy—cyclohexanone strain energy) we get a scatter diagram meaning that there is no evident correlation between ketone reactivity and the strain energy proposed by Allinger.[18]

The same type of relationship is also obtained in the inverse reaction to the addition reaction, still using cyclohexanone as reference (Table III). In Table IV, values of A and B are given for the decomposition of bisulfite addition compounds, chromic acid oxidation of secondary alcohols, and oximation in basic conditions where the reaction goes from the carbinolamine intermediate to the ketone.

The importance of such a relationship for the nucleophilic addition to carbonyl compounds is clear. Knowledge of the reactivity of one of the nucleophiles with an unknown ketone permits one to estimate the reactivity of this ketone with any of the other nucleophiles studied. Investigations are being performed to broaden the scale of ketones and nucleophiles and to gain further understanding into the factors which influence B.

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Epoxyannelation: New Reaction Path for Butadienylsulfonium Salts

Summary: Treatment of enolates from cyclic ketones and aldehydes with 1-butadienylsulfonium fluoborate yields the corresponding 1,3-cyclohexadiene 1-oxide.

Sir: Functionalized cyclohexane rings containing one or more epoxides include the prominent cytotoxic antibiotics crotopoxide[1a] and triptolide[1b] as well as the arene oxides.[1c] We wish to report a facile preparation of certain cyclohexadiene oxides, potential precursors for these biologically significant compounds.

The reaction of 1-butadienyldimethylsulfonium fluoborate (**1**) with certain ketone and aldehyde enolates affords dihydroarene oxides as the major product. The sequence depicted in Scheme I not only provides facile preparation of these oxides but also is one of the first examples of an intramolecular epoxidation with a sulfonium ylide where the sulfur is displaced from the molecule.[3,4]

Certain intramolecular Darzens condensations using chloroacrylates[5a] or 1,4-dichlorobutan-2-one[5b] with enolates also afford epoxides. The substituent patterns of these Darzens epoxides differ from the products reported here. This process has been termed epoxyannelation.[5b]

Scheme I