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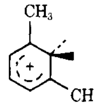
(12) It should be commented that Beauchamp and co-workers (ref. 3b) observe the exchange of only a single ring proton upon reaction of *m*-xylene with D_2O under ICR conditions. This would seem to imply that the



ion is the true ground state form of a protonated aromatic, an observation which is at odds with the results of the STO-3G calculations, which suggests the energy of such a structure to be 2.0 kcal/mol above the ion proposed here. We can think of no explanation for this discrepancy.

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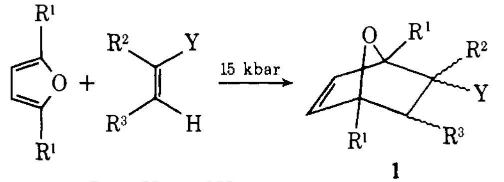
Organic Reactions at High Pressure. Cycloadditions with Furans[1]

Sir:

The 7-oxabicyclo[2.2.1]heptyl system has been employed in synthetic[2] and mechanistic[3] organic chemistry as well as applied chemistry.[4] The most straightforward approach to the construction of the 7-oxabicyclo[2.2.1]hept-5-ene framework (**1**) takes advantage of the Diels-Alder reaction between furan and a suitable dienophile.[5] Unfortunately, due to the aromatic character of furan[6] and the strain of the bicyclo[2.2.1]heptane system,[7] the cycloadducts are rather sensitive thermally toward reversal to starting materials. Consequently, only with the use of very reactive dienophiles (such as maleic anhydride and dimethyl acetylenedicarboxylate) can respectable yields of product be attained. In this communication we report the successful utilization of monoactivated dienophiles when the reactions are conducted at ~15 000 atm pressure[8] (15 kbar) and room temperature (eq 1).



(1)

1

R^1 = H or CH_3
R^2 = H or CH_3
R^3 = H, CH_3, or CO_2R
Y = CN, CO_2R, CHO, or $COCH_3$

We have previously described the results of our investigation of cycloadditions of enamines and dienamines which demonstrated the advantages of 8-20 kbar pressure, particularly in those cases where the application of heat to promote a sluggish reaction caused the destruction of the reactants.[9] Prior studies[10-12] indicated that cycloadditions between furans and ethylenes activated by only one electron withdrawing substituent take place slowly and with poor to mediocre yields when carried out at ambient pressure. We have reexamined several of these reactions at 15 kbar pressure and found that, except in those instances where both steric and electronic effects operate to retard reactivity, good yields of cycloadducts are realized. Our results are summarized in Table I.

Inspection of the data in Table I reveals that satisfactory yields (about 55%) of [4 + 2] adducts were obtained after only 4 h with acrylic dienophiles and furan (entries 1-4); in each instance approximately 1:1 ratios of exo/endo isomers were produced. Compared to thermally induced processes, the implimentation of these extremely high pressures provides substantial improvement for the conversion of reactants to products. Thus, it was reported that *5 weeks* are required to obtain a 39% yield of 2-cyano-7-oxabicyclo[2.2.1]hept-5-ene from furan and acrylonitrile.[10] Likewise, the cycloadduct from furan and methyl acrylate is produced in less than 20% yield after a month or more.[11] And in the cases of acrolein or methyl vinyl ketone and furan, only ring

Table I. Products[a] Obtained from Ultrahigh Pressure Cycloadditions[b]

Entry	R^1	R^2	R^3	Y	Hours	% yield[c,d]
1	H	H	H	CN	4	55
2	H	H	H	CO_2CH_3	4	62
3	H	H	H	CHO	4	53
4	H	H	H	$COCH_3$	4	48
5	H	H	CH_3	CN	14	0
6	H	H	CH_3	CO_2CH_3	14	6
7	H	H	CH_3	CHO	8	24
8	H	H	CH_3	$COCH_3$	8	20
9	H	CH_3	H	CO_2CH_3	8	8
10	H	CH_3	H	CHO	8	7[e]
11	H	H	CO_2CH_3[f]	CO_2CH_3	8	94[g]
12	H	H	$CO_2C_2H_5$	$CO_2C_2H_5$	8	92[g]
13	CH_3	H	H	CN	4	65
14	CH_3	H	H	CO_2CH_3	4	66
15	CH_3	H	H	CHO	4	42
16	CH_3	H	H	$COCH_3$	4	36

[a] See formula **1** for structure of product. Unless indicated otherwise, all products were composed of approximately 1:1 ratios of exo/endo isomers. [b] All reactions were carried out at 15 kbar and room temp; the concentrations of the reactants were nominally 3 M in methylene chloride. [c] Yields are based on distilled materials unless indicated otherwise. Reaction conditions have not been optimized; in addition to product, only starting materials were present at the conclusion of the reaction. [d] Satisfactory analytical and spectral data were obtained for each product. [e] A substantial amount of polymeric material was also produced. [f] In this case R^3 is cis to Y in dienophile (eq 1). [g] Crude yield; NMR spectrum indicated material to be of very high purity. Product reversed to starting materials during attempted distillation. See text for stereochemistry of adduct.

substitution products are obtained.[12] Clearly, this special high pressure technique is the method of choice for the synthesis of these heterobicyclic materials.

In contrast to the success achieved with the acrylic dienophiles, the crotonic dienophiles gave relatively low yields of cycloadducts (entries 5-8). The reductions in yields are attributable to the fact that the β-methyl group introduces steric hindrance to the transition state and also inductively contributes electron density to the dienophile, thus acting in opposition to the electron-withdrawing α-substituent and retarding the rate of reaction. When two β-methyl groups are incorporated on the dienophile (as with methyl senecioate or mesityl oxide) no reactions were observed. The argument employed for the results with the crotonic dienophiles also serves to rationalize the low yields of cycloadducts obtained with the methacrylic dienophiles (entries 9 and 10). Additional evidence in support of the electronic contribution of a β-substituent is available from entries 11 and 12. In these reactions the β-carboalkoxy group enhances the dienophilicity by induction, and appropriately, excellent yields of cycloadducts were obtained;[13] for the thermal reactions the conversions are quite inefficient.[14] In addition, under the high pressure conditions employed the stereochemical integrity of the dienophile was maintained in the cycloadducts: only the endo-cis isomer was produced from dimethyl maleate and furan, and the trans isomer was the sole product from diethyl fumarate and furan. Unlike the high yields obtained with dimethyl maleate or diethyl fumarate and furan, no reactions were detected with furan and either *cis*- or *trans*-1,2,dichloro- or tetrachloroethylene.[15]

Finally, the effects of substituents on the furan nucleus were studied. For the reactions involving 2,5-dimethylfuran (entries 13-16) good yields of adducts (as approximately 1:1 ratios of exo/endo isomers) were realized. In these cases the methyl groups inductively augment the reactivity of the diene by rendering it more electron rich than furan itself, but they also impede the cycloaddition process in a steric fashion; the net result is that the yields of adducts from furan or 2,5-dimethylfuran with acrylic dienophiles are similar, implicating that the electronic and steric effects of the methyl groups are of comparable magnitude.[16] We have also investigated the reactions of furfural and methyl furoate with various dienophiles; both electron rich (i.e., ethyl vinyl ether) and electron poor (i.e., dimethyl acetylenedicarboxylate) dienophiles failed to engage in cycloadditions with these dienes, only starting materials being recovered.

In conclusion, the utilization of pressures in the 8-20 kbar range has proved to be an extremely valuable technique for effecting chemical reactions in which the products are thermally labile (such as **1**).

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Solvent Isotope Effect in Inorganic Pyrophosphatase-Catalyzed Hydrolysis of Inorganic Pyrophosphate

Sir:

Phosphate monoester dianions are generally thought to hydrolyze via an S$_N$1 (P), metaphosphate, mechanism characterized by, among other properties, a kinetic solvent isotope effect of, or close to, one.[2] We report here kinetic solvent isotope studies on the simple, Mg^{2+}-catalyzed, and yeast inorganic pyrophosphatase (PPase) (EC 3.6.1.1)-catalyzed hydrolysis of inorganic pyrophosphate (PP_i), and on some detailed models for the mechanism of the enzyme-catalyzed reaction suggested by our results.

The pH-rate profile for PPase at saturating levels of PP_i and high Mg^{2+} concentration shows a bell-shaped curve (Figure 1), with a maximum at pH 7.05 ± 0.05, in accord with previous reports.[3] The pD-rate profile is similar, but the maximum is shifted to pD 7.50 ± 0.05. Shifts of this magnitude are common in comparing pH- and pD-rate profiles.[5a] In the ranges studied, comparison of k_{obsd} at pH equal to X with k_{obsd} at pD equal to $X + 0.50$ yields an average solvent isotope effect of 1.90 ± 0.05. Simple PPi hydrolysis (Figure 2) shows no isotope effect. The shape of the pH-rate profile is in accord with previous results which have been interpreted as showing that PPi trianion is less reactive than dianion, while tetranion is essentially inert.[6] The pH-rate profile for PPi hydrolysis in the presence of Mg^{2+} (Figure 2) is more complex and is discussed in detail elsewhere.[7] For the present discussion the important region is pH 6.0-7.0. Using known thermodynamic parameters for both H^+ and Mg^{2+} dissociation from PP_i,[8] it is possible to show that the rise in k_{obsd} between 6.0 and 6.5 coincides with formation of $MgP_2O_7^{2-}$ and $Mg_2P_2O_7$ so that the plateau region (6.5-7.0) in H_2O should correspond to hydrolysis of either or both of the species. Comparing k_{obsd} in the H_2O plateau region with k_{obsd} in the D_2O plateau region (pD 7.0-7.7) gives a solvent isotope for hydrolysis of the Mg^{2+} complex(es) of PPi of 1.45 ± 0.05.[9] To our knowledge this is the first significant kinetic solvent isotope effect