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Dramatic Rate Accelerations of Diels–Alder Reactions in 5 M Lithium Perchlorate–Diethyl Ether: The Cantharidin Problem Reexamined

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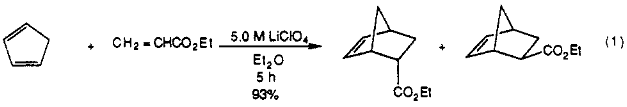
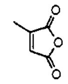
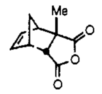
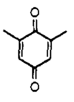
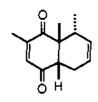
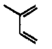
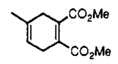
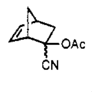
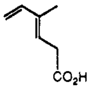
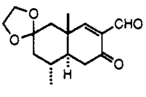
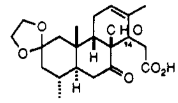
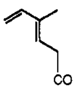
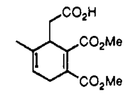
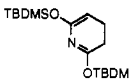
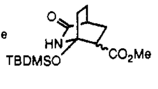
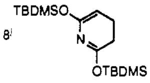
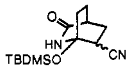
During the past 15 years, studies on the Diels–Alder reaction[1] have produced dramatic results. The pronounced rate enhancements and improved stereoselectivities observed to date have been associated with cycloadditions conducted in (1) aqueous media[2] and (2) conventional organic solvents under ultrahigh pressure (8–20 kbar).[3] While seemingly the result of two independent physical processes, it is most likely that there is a direct relationship between the rate acceleration observed when high pressure is applied to a Diels–Alder reaction and the rate enhancement observed in a solvent, like water, possessing a "high" internal solvent pressure.[4] On the basis of this supposition, it seems logical to conclude that solvents (media) that possess internal solvent pressures equal to or greater than that of water should provide comparable rate accelerations for intermolecular cycloaddition processes. Herein, we report our findings, which show that 5.0 M lithium perchlorate in diethyl ether[5] is a powerful medium for facilitating [4 + 2] cycloaddition reactions. *Diels–Alder adducts that hitherto were inaccessible via conventional means can now be realized through the agency of this remarkable medium.*

In a preliminary study, ethyl acrylate, dissolved in a 5.0 M solution of lithium perchlorate[7] in diethyl ether, was treated with 1.0 equiv of cyclopentadiene (eq 1). After 5 h at ambient temperature and pressure, a 93% isolated yield of cycloadducts possessing an endo:exo ratio of 8:1 was obtained. For comparison purposes, the reaction between cyclopentadiene and ethyl acrylate was conducted in water. After 5 h, a 73% yield of cycloadducts possessing an endo:exo ratio of 4:1 was obtained. The enhanced endo selectivity and reaction rate observed above in 5.0 M $LiClO_4/Et_2O$, coupled with the fact that the vast majority of organic compounds are insoluble in water and that water precludes the use of water-sensitive substrates, led us to explore further the potential of this unique solvent system for the Diels–Alder reaction.[8]



(1)

Table I. [4 + 2] Cycloadditions Employing 5.0 M Lithium Perchlorate in Diethyl Ether[a]

entry	diene	dienophile	product	time	% yield[b]
1				3 h	90[c]
2				15 min	80[d]
3		$MeO_2CC\equiv CCO_2Me$		12 h	94[e]
4		$CH_2{=}C(OAc)CN$		4 h	79[f]
5				5 h	85[g,h]
6		$MeO_2CC\equiv CCO_2Me$		24 h	68[i]
7[j]		$CH_2 = CHCO_2Me$		5 h[k]	80[l,m]
8[j]		$CH_2 = CHCN$		3 h[k]	78[n,o]

[a] All reactions were performed 1.0 M in diene and 0.2 M in dienophile unless stated otherwise. [b] Isolated yields. [c] Yield of 94% after 24 h at 60 °C (neat).[14] [d] Yield of <20% after 24 h in water. [e] Yield of 50% after 12 h in water. [f] Yield of 27% after 24 h in water. [g] C(14)-βH:C(14)αH ratio equal 2.3:1. [h] Yield of 90% after 4.5 in water, employing the diene carboxylate. Use of the dienoic acid in water was slow. [i] Yield of 60% after 24 h in water. [j] 3.0 equivalents of diene were employed. [k] The reaction is worked up with methanol to cleave the imino ether. [l] Yield of 74% (endo:exo ratio 1:11.5) after 72 h in benzene at 60 °C.[9] [m] An endo:exo ratio of 2.9:1 was observed in 5.0 M $LiClO_4$–Et_2O. [n] An endo:exo ratio of 1:3.7 was observed in 5.0 M $LiClO_4$–Et_2O. [o] Yield of 73% (endo:exo ratio of 1:9) after 48 h in benzene at 60 °C.[9]

Table II. Reaction of Dienophile **1** with Furan at Ambient Temperature and Pressure in Varying Concentrations of Lithium Perchlorate in Diethyl Ether[a]

molarity	% yield[b]	ratio (**2**:**3**)[c]
1.0	15	85:15
2.0	22	87:13
3.0	36	86:14
4.0	62	83:17
5.0	70	85:15

[a] All reactions were run 0.5 M in dienophile for 9.5 h in the presence of 10 equiv of furan. [b] Isolated yields. [c] Ratios determined by ^1H NMR.

The procedure detailed above employing 5.0 M $LiClO_4$ in diethyl ether is applicable to a variety of substrates (Table I). Note that all reactions are homogeneous and were conducted at ambient temperature and pressure. All reactions exhibited pronounced rate accelerations and improved yields. In those cases involving water-sensitive substrates (entries 1, 7, and 8), reactions proceeded smoothly in excellent yield. For example, the [4 + 2] cycloaddition of the aza diene in entry 7 with methyl acrylate is complete after 5 h in 5.0 M $LiClO_4/Et_2O$, giving rise to an 80%

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(1) Sauer, J.; Sustmann, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 799.

(2) For examples, see: (a) Rideout, D. C.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7816. (b) Grieco, P. A.; Garner, P.; He, Z. *Tetrahedron Lett.* **1983**, *24*, 1897. (c) Breslow, R.; Maitra, U.; Rideout, D. *Tetrahedron Lett.* **1983**, *24*, 1901. (d) Grieco, P. A.; Yoshida, K.; Garner, P. *J. Org. Chem.* **1983**, *48*, 3137.

(3) Dauben, W. G.; Kozikowski, A. P. *J. Am. Chem. Soc.* **1974**, *96*, 3664. Also, see: Van Eldik, R.; Asano, T.; Le Noble, W. J. *Chem. Rev.* **1989**, *89*, 549 and references cited therein.

(4) Cf.: McCabe, J. R.; Eckert, C. A. *Acc. Chem. Res.* **1974**, *7*, 251.

(5) Lithium perchlorate solutions in diethyl ether have previously been employed to accelerate reactions with polarized transition states.[6] In contrast, the rates of intermolecular Diels–Alder reactions are essentially independent of solvent polarity, varying at most by 1 order of magnitude.

(6) Over 30 years ago, Winstein (Winstein, S.; Smith, S.; Darwish, D. *J. Am. Chem. Soc.* **1959**, *81*, 5511) observed that the ionization rate of *p*-methoxyneophyl *p*-toluenesulfonate in 0.1 M $LiClO_4$–Et_2O increased by a factor of 10^5. Similarly, Pocker has reported (Pocker, Y.; Buchholz, R. F. *J. Am. Chem. Soc.* **1970**, *92*, 2075) that use of ca. 5.0 M $LiClO_4$–Et_2O increases the rate of ionization of trityl chloride by 7.0 x 10^9.

(7) Commercially available (Aldrich) lithium perchlorate was dried under high vacuum (P_2O_5 trap) at 160 °C for 48 h. Lithium perchlorate is thermally stable at or above its melting point of 247 °C.

(8) In a recent study, Jaeger (Jaeger, D. A.; Tucker, E. C. *Tetrahedron Lett.* **1989**, *30*, 1785) observed that the fused salt ethylammonium nitrate gave endo selectivity enhancements for the Diels–Alder reaction between cyclopentadiene and methyl acrylate; however, the reaction rate was 1 order of magnitude slower than the corresponding reaction in water.

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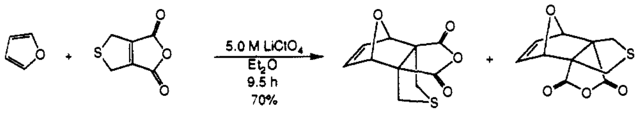
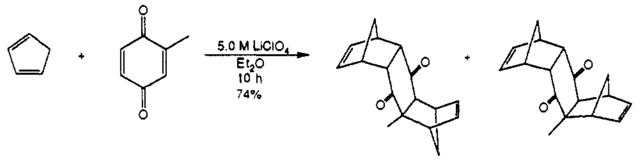
yield of cycloadduct, whereas the same reaction in benzene[9] requires 72 h at 60 °C in order to realize a 74% yield of product.

In order to fully define the scope of 5.0 M lithium perchlorate in diethyl ether as a medium for effecting Diels–Alder reactions, we set out to examine the reaction of furan with 2,5-dihydrothiophene-3,4-dicarboxylic anhydride (**1**). Furan is a poor Diels–Alder diene due to its aromaticity and generally requires pressures in the range of 10–20 kbar to effect cycloaddition.[10] High temperatures are not compatible with furan Diels–Alder chemistry since the cycloaddition products derived from furan undergo cycloreversion at high temperatures. In his classic synthesis of cantharidin,[11] Dauben found that the reaction of furan with dienophile **1**[12] in methylene chloride required 6 h under 15 kbar of pressure in order to realize an 85:15 mixture of cycloadducts **2** and **3**. In sharp contrast, the Diels–Alder reaction between furan and dienophile **1** in 5.0 M lithium perchlorate in diethyl ether proceeded at ambient temperature and pressure, giving rise (70% yield) after 9.5 h to cycloadducts **2** and **3** in an 85:15 ratio. A systematic examination of this reaction confirmed a direct correlation between reaction rate and molarity, with the rate increasing on going from 1.0 to 5.0 M lithium perchlorate in diethyl ether (Table II).



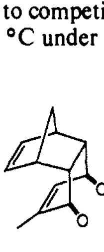
1 2 3

Equally remarkable was the observation that exposure of methylbenzoquinone to cyclopentadiene in 5.0 M lithium perchlorate in diethyl ether for 10 h at room temperature and atmospheric pressure afforded in 74% yield bis adducts **4** and **5** in a 6:1 ratio.



4 5

Admixture of cyclopentadiene and methylbenzoquinone in diethyl ether without lithium perchlorate gives rise in excellent yield to the 1:1 Diels–Alder adduct **6** with no evidence for the formation of bis adducts **4** and **5**. It is of interest to note that the formation of bis adducts **4** and **5** has been reported to occur at high pressure.[13] For example, heating a toluene solution of cyclopentadiene (large excess required due to competing diene dimerization) and methylbenzoquinone at 75 °C under 7895 atm overnight affords **4** and **5** in 60% yield.



6

The ease with which these normally demanding cycloadditions proceed points to the operation of factors that are not adequately explained in the current literature. The ability of 5.0 M $LiClO_4$–Et_2O, a unique ionic medium, to confine solute movement and hence retain solvent ordering may well be responsible for the observed rate accelerations by compressing the reactants in much the same manner as the "macroscopic" application of external pressure.[15] As the Diels–Alder reaction is known to possess a large negative volume of activation, this action would serve to raise the ground-state energy of the reactants relative to the transition state, thereby lowering the activation energy.

In conclusion, the utilization of 5.0 M lithium perchlorate in diethyl ether to promote intermolecular [4 + 2] cycloaddition at ambient temperature and pressure has been established, thus permitting the use of water-sensitive substrates and obviating the necessity of effecting these chemical reactions at high temperatures and ultrahigh pressures.

Acknowledgment. This investigation was supported by a grant from the National Science Foundation. We thank Professor Joseph J. Gajewski for helpful discussions.

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(9) Rivera, M.; Lamy-Schalkens, H.; Sainte, F.; Mbiya, K.; Ghosez, L. *Tetrahedron Lett.* **1988**, *29*, 4573.

(10) Dauben, W. G.; Krabbenhoft, H. O. *J. Am. Chem. Soc.* **1976**, *98*, 1992.

(11) Dauben, W. G.; Kessal, C. R.; Takemura, K. H. *J. Am. Chem. Soc.* **1980**, *102*, 6893.

(12) Baker, B. R.; Querry, M. J.; Kadish, A. F. *J. Org. Chem.* **1948**, *13*, 128.

(13) Srivastava, S.; Marchand, A. P.; Vidyasagar, V.; Flippen-Anderson, J. L.; Gilardi, R.; George, C.; Zachwieja, Z.; Le Noble, W. J. *J. Org. Chem.* **1989**, *54*, 247.

(14) Lal, K.; Salomon, R. G. *J. Org. Chem.* **1989**, *54*, 2628.

(15) The possibility that lithium perchlorate is stabilizing a polar transition state has not been ruled out; however, the observed rate accelerations cannot be fully accounted for by this mechanism alone.

Observations on the Activation of Mitomycin C. Requirements for C-10 Functionalization

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Mitomycin C (**1**), a proven antineoplastic agent of clinical significance,[1] is believed to require reductive activation prior to bonding to DNA.[2] Despite 25 years of intense research our understanding of the reductive process is limited. Uncertainty exists in the specific reduction and ionization states in **1** necessary for the C-1 and C-10 drug bonding steps.[2] In this communication, we report on the first use of transition-metal ions for the activation of mitomycin C. Employment of $Cr(ClO_4)_2$ as a one-electron reductant[3] has dramatically altered the reactivity pattern of the two DNA-bonding sites within **1**.[2e] Moreover, analysis of the data permitted us to propose a detailed description of the molecular events necessary for complete drug function.

Two different $Cr(ClO_4)_2$-mediated reductive techniques were developed. In the first procedure, $Cr(ClO_4)_2$ (1–2 equiv) was directly added to **1** at various pH values (Table I, entries 1–7). Important observations included the following: (1) Consumption of **1** was rapid and generated both *trans*- and *cis*-10-decarbamoyl-1-hydroxy-2,7-diaminomitosene[4] (**5**) as the major products. (2) The reaction efficiency increased at lower pH values. (3) Between pH 6.0 and 7.0, the difunctionalized mitosene adducts **3** and **5** accounted for nearly half of the product profile even though noticeable amounts of unreacted **1** remained. (4) Significant amounts of C-1 electrophilic products (i.e., **2** and **3**) were

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(1) Carter, S. K.; Crooke, S. T. *Mitomycin C. Current Status and New Developments*; Academic Press: New York, 1979.

(2) (a) Iyer, V. N.; Szybalski, W. *Science* **1964**, *145*, 55. (b) Remers, W. A. *The Chemistry of Antitumor Antibiotics*; Wiley: New York, 1979; Vol. 1, pp 221–276. (c) Franck, R. W.; Tomasz, M. In *The Chemistry of Antitumor Agents*; Wilman, D. F. V., Ed.; Blackie and Sons, Ltd.: Scotland, 1989. (d) Fisher, J. F.; Aristoff, P. A. *Prog. Drug Res.* **1988**, *32*, 411. (e) Tomasz, M.; Lipman, R.; Chowdary, D.; Pawlak, J.; Verdine, G.; Nakanishi, K. *Science* **1987**, *235*, 1204. (f) Teng, S. P.; Woodson, S. A.; Crothers, D. M. *Biochemistry* **1989**, *28*, 3901. (g) Cera, C.; Egbertson, M.; Teng, S. P.; Crothers, D. M.; Danishefsky, S. J. *Ibid.* **1989**, *28*, 5665.

(3) (a) Kochi, J. K.; Singleton, D. M.; Andrews, L. J. *Tetrahedron* **1968**, *24*, 3503. (b) Kochi, J. K.; Powers, J. W. *J. Am. Chem. Soc.* **1970**, *92*, 136.

(4) Andrews, P. A.; Pan, S.-S.; Bachur, N. R. *J. Am. Chem. Soc.* **1986**, *108*, 4158.

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