Communications

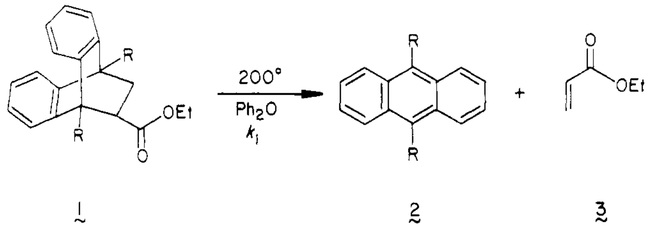
Diene-Substituent Effects on the Rate of the Retro-Diels–Alder Reaction. Cycloreversion Reactivity Varying over a Range of Five Powers of Ten

Summary: The retro-Diels–Alder reaction of anthracene cycloadducts is influenced by diene substituents in the following ways: (1) electron-donating groups increase the reaction rate, and the accelerating effect is subject to geometric modulation; (2) electron-withdrawing groups may decrease or increase the reaction rate, although the effect is rarely large; and (3) steric acceleration is relatively small and demonstrates an unprecedented bell-shaped structure–reactivity profile.

Sir: The retro-Diels–Alder (rDA) reaction, which is the reverse of the well-known Diels–Alder 4 + 2 cycloaddition reaction, has proven useful both as a synthetic tool[1] and as a mechanistic probe.[2] However, while the use of anionic substitution[3] and acid catalysis[4] has made some cycloreversions accessible near room temperature, the rate effects of neutral dienophile substituents have only recently been examined.[5] A systematic survey of diene substituents on the retro-Diels–Alder reaction has not been reported to date.[6] Such information is essential to our group's work on the design of cycloaddition/cycloreversion-based catalysts,[7] as well as of potential utility in rDA-based synthetic schemes.

We now report[8] that strain effects by diene substituents play a relatively minor role in achieving significant cycloreversion accelerations; however, *the introduction of polar, charge-neutral diene substituents results in reaction rates varying over a range of 10^5.*

For this work, we prepared cycloadducts **1a–x**; while the syntheses of many adducts were straightforward, a few comments are in order.[9] We were able to prepare anthracenes **2b**, **2c**, **2e**,[10] and the previously unknown 9,10-diiodoanthracene (**2r**) by treatment of 9,10-dilithioanthracene[11] with appropriate electrophiles. A literature procedure for the synthesis of 9,10-diacetylanthracene (**2g**) gives instead the 1,5-isomer;[12] we successfully prepared anthracene **2g** by the reaction of methyl ester **2h** with an excess of methyllithium. Adduct **1u** was prepared by reaction of ethyl acrylate with the corresponding anthracenophane **2u**, whose synthesis has been reported previously;[13] anthracenophane **2v** and adduct **1v** were prepared similarly. Most adducts were prepared by direct condensation of the appropriate 9,10-disubstituted anthracene with ethyl acrylate; a few (**1d**, **1s**, and **1r**) were made by reaction of the anthracene with acryloyl chloride, followed by ethanol. Adducts **1n**, **1o**, and **1p** were prepared by functional-group manipulation of adducts **1m**, **1q**, and **1o**, respectively.



In each case, cycloreversion was accomplished by heating an approximately 1.2×10^{-4} M solution of the adduct in dry diphenyl ether at 200 ± 1 °C.[14] At various times, an aliquot was removed and cooled to room temperature, and the concentration of the anthracene product was determined by measuring the solution's absorbance at that anthracene's long-wavelength λ_{max} (shown in Table I). In two cases (**1n** and **1o**), oxidation of the anthracene under the conditions of the cycloreversion was extremely fast; the formation of oxidized products at 326 and 304 nm, respectively, was monitored instead.[15]

From the data compiled in Table I, several trends may

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[1] For synthetic reviews of the retro-Diels-Alder reaction, see: (a) Ripoll, J.-L.; Rouessac, A.; Rouessac, F. *Tetrahedron* **1978**, *34*, 19. (b) Sauer, J. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 229. (c) Kwart, H.; King, K. *Chem. Rev.* **1968**, *68*, 415. (d) Lasne, M.-C.; Ripoll, J.-L. *Synthesis* **1985**, 121.

[2] For mechanistic reviews of the retro-Diels–Alder reaction, see: (a) Reference 1c. (b) Smith, G. G.; Kelly, F. W. *Prog. Phys. Org. Chem.* **1971**, *8*, 201. (c) Sauer, J.; Sustmann, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 779.

[3] (a) Knapp, S.; Ornaf, R. M.; Rodriques, K. E. *J. Am. Chem. Soc.* **1983**, *105*, 5494. (b) Papies, O.; Grimme, W. *Tetrahedron Lett.* **1980**, *21*, 2799. (c) Rajanbabu, T. V.; Eaton, D. F.; Fukunaga, T. *J. Org. Chem.* **1983**, *48*, 652. (d) VaraPrasad, J. V. N.; Iyer, P.; Pillai, C. N. *J. Org. Chem.* **1982**, *47*, 1380. (e) Bowman, E. S.; Hughes, G. B.; Grutzner, J. B. *J. Am. Chem. Soc.* **1976**, *98*, 8273. (f) Papies, O.; Grimme, W. *Tetrahedron Lett.* **1978**, 2201.

[4] (a) Bunnelle, W. H.; Shangraw, W. R. *Tetrahedron* **1987**, *43*, 2005. (b) Grieco, P. A.; Parker, D. T.; Fobare, W. F.; Ruckle, R. *J. Am. Chem. Soc.* **1987**, *109*, 5859.

[5] Nanjappan, P.; Czarnik, A. W. *J. Org. Chem.* **1986**, *51*, 2851.

[6] Substituent effects in the bicyclooctadiene series are being concurrently investigated by Prof. D. Hasselman, Ruhr-Universitat Bochum, Lehrstuhl fur Organische Chemie II, to whom we are grateful for sharing his results with us.

[7] (a) Czarnik, A. W. *Tetrahedron Lett.* **1984**, *25*, 4875. (b) Nanjappan, P.; Czarnik, A. W. *J. Am. Chem. Soc.* **1987**, *109*, 1826.

[8] Presented at the first Euchem conference on the Diels–Alder reaction, June 29–July 2, 1987, Assisi, Italy.

[9] Complete syntheses for these structurally simple compounds will be presented in the full paper.

[10] 9,10-Bis(trimethylsilyl)anthracene (**2e**), which may be prepared by the methods of Harvey (Cho, H.; Harvey, R. G. *J. Org. Chem.* **1975**, *40*, 3097), Lehmkuhl (Lehmkuhl, H.; Skakoor, A.; Mehler, K.; Kruger, C.; Angermund, K.; Tsay, Y.-H. *Chem. Ber.* **1985**, *118*, 4239), and Roberts (*J. Organomet. Chem.* **1976**, *110*, 281), can also be prepared by the reaction of 9,10-dilithioanthracene with trimethylsilyl chloride in the presence of TMEDA (Alonso, T.; Harvey, S.; Junk, P. C.; Raston, C. L.; Skelton, B. W.; White, A. H. *Organometallics*, accepted for publication).

[11] (a) Mikhailov, B. M. *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk* **1948**, 420; *Chem. Abstr.* **1949**, *43*, 2096. (b) Herrmann, U.; Tummler, B.; Maass, G.; Tse Mew, P. K.; Vogtle, F. *Biochemistry* **1984**, *23*, 4059.

[12] Kamiya, I.; Sugimoto, T. *Chem. Lett.* **1978**, 335.

[13] Vogtle, F.; Tse Mew, P. K. *Angew. Chem., Int. Ed. Engl.* **1978**, *1*, 17. For detailed conditions in related reactions, see: Chung, J.; Rosenfeld, S. M. *J. Org. Chem.* **1983**, *48*, 387.

[14] The determination of first-order rate constants and of kinetic activation parameters (reported as ± 1 standard deviation) was accomplished by using the computer program LSTSQ, available from Serena Software, 489 Serena Lane, Bloomington, IN 47401. Molecular mechanics programs adapted from Allinger's *MMP1* were also obtained from Serena Software; this version (name: MMPMI) with the accompanying graphics routine was run on an IBM-AT microcomputer.

[15] Rapid oxidation of anthracenes **1n** and **1o** was confirmed by adding a sample of each anthracene to deoxygenated diphenyl ether at 200 °C. The UV spectrum, taken within 15 s, in each case showed no anthracene absorptions, only peaks at 326 and 304 nm, respectively.

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Table I. First-Order Rate Constants of Retro-Diels–Alder Reactions at 200 °C in Diphenyl Ether

R	compd	UV of anthracene[a] (λ_{max} is underlined)	% of reaction used to calculate rate constant	$10^5 k_1$, s^{-1}	half-life, min	rel rate	σ_p
H	**1a**	328, 344, $\underline{362}$, 382	8–98	1.72	672	1.00	0.00
Me	**1b**	346, 362, $\underline{382}$, 404	2–85	3.87	298	2.25	–0.17
Et	**1c**	346, 362, $\underline{382}$, 404	4–95	34.7	33.0	20.2	–0.15
i-Pr	**1d**	346, 362, $\underline{382}$, 404	1–94	13.6	84.9	7.91	–0.15
$Si(CH_3)_3$	**1e**	318, 344, $\underline{362}$, 382	13–81	4.63	249	2.69	–0.07
CHO	**1f**	$\underline{430}$ (br)	17–93	8.32	139	4.84	0.22
$COCH_3$	**1g**	338, 354, $\underline{372}$, 392	14–80	3.10	372	1.80	0.50
CO_2CH_3	**1h**	338, 352, $\underline{370}$, 390	2–89	0.415	2780	0.24	0.39
$OCOCH_3$	**1i**	340, 358, $\underline{376}$, 398	2–92	3.40	340	1.98	0.31
SCH_3	**1j**	372, 390, $\underline{412}$	6–95	34.0	34.0	19.8	0.00
OCH_3	**1k**	352, 368, $\underline{386}$, 408	17–86	69.0	16.7	40.1	–0.27
OPh	**1l**	304, 364, $\underline{384}$, 406	22–91	198	5.83	115	–0.32
$OSi(CH_3)_3$	**1m**	358, 378, $\underline{404}$, 428	14–93	453	2.55	263	*b*
OH	**1n**	*d*	*c*	2420	0.48	1410	–0.37
NH_2	**1o**	382, $\underline{402}$	32–96	4000	0.29	2330	–0.66
$N(CH_3)_2$	**1p**	338, 378, $\underline{398}$	4–94	239	ca. 2.2	140	–0.83
NO_2	**1q**	340, 354, $\underline{372}$, 394	*c*	0.031	37300	0.02	0.78
I	**1r**	356, 372, 392, $\underline{416}$	3–88	1.40	825	0.81	0.30
Br	**1s**	350, 366, $\underline{386}$, 408	3–88	0.808	1429	0.47	0.27
Cl	**1t**	348, 366, $\underline{386}$, 408	3–73	1.39	831	0.81	0.23
$-CH_2S(CH_2)_8SCH_2-$	**1u**	352, 370, 388, $\underline{412}$	18–94	40.3	28.7	38.8	*b*
$-CH_2S(CH_2)_{10}SCH_2-$	**1v**	352, 368, 388, $\underline{410}$	15–92	26.1	44.3	25.2	*b*
CH_2SCH_3	**1w**	350, 368, 386, $\underline{408}$	15–95	26.4	43.8	29.2	*b*
$CH_2SC(CH_3)_3$	**1x**	350, 368, 386, $\underline{408}$	14–87	48.4	23.9	46.5	*b*

[a] Spectrum in diphenyl ether; λ values are reported ±1 nm. [b] No known substituent constant. [c] k_1 was extrapolated from the temperature dependence. [d] Due to rapid oxidation, only a peak at 326 nm due to anthraquinone is observed.

be identified. First, electron-donating groups accelerate the cycloreversion reaction, a fact that is corroborated by comparing entries **1b** and **1j–p** with reference entry **1a**. This is a result predicated by previous studies, in which accelerations by methoxy[16] and siloxy[3b] substituents were observed. It is of interest that, while not linear, a direct relationship exists between electron-donating ability (as measured by the Hammett σ_p constant)[17] and the rate of cycloreversion in the series R = H < Me < OCH_3 < OPh < OH < NH_2. The pair NMe_2 and NH_2 would seem to constitute a notable exception; the NMe_2 group is more electron releasing than the NH_2 group, yet adduct **1p** reacts over 16 times more slowly than does adduct **1o**. We suggest that the larger size of the more electron donating dimethylamino group forces it out of planarity with the anthracene ring due to repulsion with the peri hydrogens;[18a] X-ray structures of 9-substituted and 9,10-disubstituted anthracenes reveal such a nonplanarity in the case of two-dimensional substituents such as the nitro group.[18b–d] Such a deconjugation in the dimethylamino adduct would lessen any p–π overlap and thereby lessen resonance interactions. In support of this idea, we have measured the oxidation potentials of anthracenes **2o** and **2p** by cyclic voltammetry; as anticipated, while *N*,*N*-dimethylaniline is easier to oxidize than is aniline itself, 9,10-bis(*N*,*N*-dimethylamino)anthracene (**2p**) is *harder* to oxidize than is 9,10-diaminoanthracene (**2o**).[19] It therefore seems clear that the transition structure for cycloreversion reflects the aromatic character of the anthracene product to a significant extent.

Second, we find that electron-withdrawing groups do *not* decelerate cycloreversion reactions greatly, if at all, as might have been expected. A comparison of adducts **1f–i** and **1r–t** to reference adduct **1a** makes this point succinctly. In each case, reaction rates differ only by a factor of 5 at most, in clear variance with the large effects afforded by electron-donating groups. The single exception is the dinitro adduct **1q**, which cycloreverts 46 times more slowly than adduct **1a** and fully 1.3 × 10^5 times more slowly than the diamino adduct (**1o**). This range of reactivity is quite exceptional; while dinitro adduct **1q** cycloreverts at 200 °C with a half-life of over 3 weeks,[20] diamino adduct **1o** cycloreverts with a half-life of 17 s!

Third, steric effects on the retro-Diels–Alder reactions of anthracene cycloadducts are documented by comparing entries **1a–e**, which reveal an unprecedented bell-shaped pattern. While 9,10-dimethylanthracene is much more reactive toward cycloaddition reactions than is anthracene itself,[21] adduct **1b** cycloreverts only about twice as fast as does adduct **1a**. The rate increases rather dramatically on going to diethyl substituents, for reasons that are not immediately clear; however, progression to the next member of this homologous series, diisopropyl, yields a rate *decrease*. While it would have been optimal to compare

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(16) Sauer, J. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 211 (esp. see p 230).

(17) The Hammett σ_p constant is only one of several specialized σ parameters that could be used to characterize substituents (see: Hine, J. In *Structural Effects on Equilibria in Organic Chemistry*; Robert E. Krieger: Huntington, NY, 1981; Chapter 3). However, because it reflects a commonly accepted ranking of the electron-donating/withdrawing ability of these groups, it is an appropriate yardstick for comparison.

(18) (a) Molecular mechanics calculations predict that (i) both dimethylamino groups in **2p** are roughly perpendicular to the anthracene in the ground state and (ii) a 180° rotation of one perpendicular dimethylamino group passes over a 23 kcal/mol energy barrier. (b) Trotter, J. *Can. J. Chem.* **1959**, *37*, 351. (c) Trotter, J. *Can. J. Chem.* **1959**, *37*, 825. (d) Bart, J. C. J.; Schmidt, C. M. J. *Isr. J. Chem.* **1971**, *9*, 429.

(19) An acetonitrile solution with tetrabutylammonium hexafluorophosphate as the supporting electrolyte was used to establish chemically irreversible oxidations at 1.20 V (aniline), 0.95 V (*N*,*N*-dimethylaniline), 0.18 V (9,10-diaminoanthracene), and 0.55 V (9,10-bis(dimethylamino)anthracene) vs a Ag/AgCl reference. A platinum electrode was used at a scan rate of 100 mV/s.

(20) Because of the very slow reaction rate when adduct **1q** was used ($t_{1/2} \simeq$ 3.5 weeks at 200 °C), oxidation of the 9,10-dinitroanthracene product became marginally competitive with cycloreversion; accurate values for rate constants (and therefore activation parameters) were therefore difficult to obtain, and the values are estimated to be accurate to within ±25%.

(21) 9,10-Dimethylanthracene reacts with 1,1-dicyanoethylene from 500 to 700 times faster (depending on solvent) than does anthracene itself at 20 °C (cf. ref 2c, p 798).

Table II. Kinetic Activation Parameters for Some Representative Substituents in the Retro-Diels–Alder Reaction of Anthracene Adducts in Diphenyl Ether

R	compd	$\Delta H^‡$, kcal/mol	$\Delta S^‡$, eu	T(av), °C
H	**1a**	34.8 ± 1.4	−7.9 ± 2.7	230
Me	**1b**	37.8 ± 1.9	0.4 ± 3.9	223
Et	**1c**	36.1 ± 3.5	−0.1 ± 7.2	210
i-Pr	**1d**	35.7 ± 0.9	−3.7 ± 1.9	220
CHO	**1f**	40.0 ± 1.1	6.5 ± 2.3	215
OCH_3	**1k**	32.3 ± 1.0	−5.5 ± 2.0	215
OPh	**1l**	36.2 ± 1.2	4.6 ± 2.6	195
OH	**1n**	49.8 ± 4.6	39 ± 10	165
$-CH_2S(CH_2)_8SCH_2-$	**1u**	32.6 ± 0.4	−6.0 ± 0.9	210
$-CH_2S(CH_2)_{10}SCH_2-$	**1v**	37.2 ± 4.2	3.1 ± 8.5	215

these data with the di-*tert*-butyl adduct, we have to date been unable to prepare the highly strained 9,10-di-*tert*-butylanthracene. Instead, one may consider (with appropriate reservation)[22] the reactivity of disilyl adduct **1e**, which is again slower than diisopropyl adduct **1d**. Our analysis of this bell-shaped reactivity relationship centers on the question: how much does the transition structure "know" about steric problems in the anthracene it is going to? It is reasonable to conclude, on the basis of molecular-mechanics calculations and examinations of space-filling models, that increasing steric bulk of the substituents results in greater strain energies of *both* adducts and anthracenes. However, steric strain in the adducts, in which a "gear-like" orientation between substituent and adduct framework can exist, is less than strain in the anthracenes, in which bad contacts with the peri hydrogens cannot be avoided *beginning with the isopropyl group*. In other words, at some hypothetical point between ethyl and isopropyl groups, the generation of strain in the transition structure wins out over the release of strain in the starting material, and the reaction slows. On the basis of entries **1u–x**, our notion that strain induced by bridging substituents would accelerate cycloreversions significantly appears unfounded, perhaps for the same reasons described above.

One additional set of results is pertinent to a discussion of the mechanism of the retro-Diels–Alder reaction. As shown in Table II, the activation entropies of most cycloreversion reactions fall near 0 eu, as is consistent with the picture of the retro-Diels–Alder transition structure resembling that of the adduct.[23] However, cycloreversion of the dihydroxy adduct **1n** shows surprisingly large positive values for both $\Delta H^‡$ and $\Delta S^‡$. The observation that cycloreversion of the dihydroxy adduct uniquely exhibits a substantial deceleration in less polar solvent[24] suggests that deprotonation (either full or partial) of a tertiary alcohol in **1n** is the rate-limiting step. Dramatic acceleration of the retro-Diels–Alder reaction by alkoxide substituents has been reported previously by Grimme,[3b] and we observe the same effect. A THF solution of dihydroxy adduct **1n** at reflux (66 °C) shows no (less than 1%) cycloreversion after 120 h. After cooling to room temperature, addition of excess NaH results in rapid cycloreversion ($t_{1/2}$ about 11 min). It therefore seems likely that the activation parameters determined for **1n** reflect a deprotonation step rather than a cycloreversion.

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[22] Because the Si–C bond is longer than the C–C bond, the purely steric effect of a $Si(CH_3)_3$ group is expected to be smaller than that of a $C(CH_3)_3$ group; the inductive electronic effects are predicted to be similar, based on σ_p values. It is difficult to predict what the resonance effect of the vacant silicon d orbital would be, although as a rDA dienophile substituent, $Si(CH_3)_3$ is faster than $C(CH_3)_3$ by about 22-fold at 250 °C (cf. ref 4).

[23] It is sometimes said that the forward Diels–Alder reaction is "entropy late and enthalpy early"; the converse would state that the retro-Diels–Alder is "enthalpy late and entropy early".

[24] When pentadecane (nonpolar) and diphenyl ether (more polar) are used at 200 °C, the relative reaction rates are as follows: R = Et, 1.00, 1.38; R = NMe_2, 1.00, 1.09; R = $OSiMe_3$, 1.00, 1.19; R = OH, 1.00, 12.0. It was not possible to obtain a highly accurate rate constant for cycloreversion of the R = NH_2 adduct at 200 °C in pentadecane because oxidation was no longer very fast as compared to cycloreversion. By following the appearance and disappearance of the peak at 402 nm due to diaminoanthracene (maximum absorbance at 35 s), we could then use a curve-fitting algorithm to estimate the rate constant for cycloreversion in pentadecane as 3.5×10^{-2} s^{-1}. This number is probably indistinguishable from the rate constant determined for 9,10-bis(dimethylamino)anthracene (4.0×10^{-2} s^{-1}).

Anionic Cyclizations of α-Alkoxy Lithiums. New, Stereoselective Routes to Substituted Tetrahydrofurans

Summary: Treatment of the (tri-*n*-butylstannyl)methyl ethers of alkyl allyl carbinols with *n*-BuLi in THF at −78 °C gives the corresponding α-alkoxy lithiums. On warming, these species undergo anionic cyclization to afford cis-2,4-disubstituted tetrahydrofurans. A useful variant of this method, which employs allylic ethers as cyclization terminators, is also described.

Sir: The cyclization reactions of 5-hexenyl radicals have formed the basis for a wide variety of synthetic methods introduced during recent years.[1] It has been known for some time that 5-hexenyl carbanions can undergo a similar

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[1] Hart, D. J. *Science* (*Washington D. C.*) **1984**, *223*, 883.

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