Ultracentrifuge-mediated Diels–Alder Reaction in a Two-phase System of Water and Chloroform

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Dramatic acceleration of the Diels–Alder reaction of acrylate ester or methacrolein with cyclopentadiene has been observed under ultracentrifugation conditions in the presence of water, when water–$CHCl_3$ two-phase system was employed. The Diels–Alder reaction proceeds in the lower organic phase under ultracentrifugation-induced high pressure with the upper water phase acting like a weight.

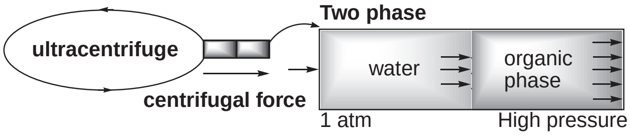
Many organic transformations can be accelerated by high pressure.[1] As special apparatus is usually required to perform such high-pressure reactions, the development of convenient and easy methods for the realization of high pressure is desirable. Along these lines, we have been developing a new high-pressure method induced by water-freezing (200 MPa, $-20\,^{\circ}C$), which has been successfully applied to the Michael reaction of alcohols and α,β-enones,[2] the Baylis–Hillman reaction,[3] the direct catalytic asymmetric aldol,[4] and three-component Mannich reactions.[5]

Ultracentrifugation, on the other hand, is known to produce extremely high centrifugal forces, which could be utilized for the generation of high pressure. Bergman and Dolata have reported the application of ultracentrifugation to the Diels–Alder reaction of furan and maleic anhydride.[6] They showed that a higher yield (53%) was obtained under ultracentrifugation than under ambient pressure (40%), and that the reaction proceeds faster at the bottom of the reaction tube than at the top. As the reported reaction is restricted in scope to only this one example, and there are no other systematic investigations of high-pressure reactions.

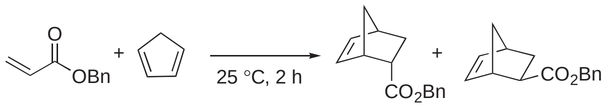
On the other hand, Diels–Alder reaction is known to be accelerated in water because of the hydrophobic effect. We have found that the application of an organic–water two-phase system to the Diles–Alder reaction under ultracentrifugation can dramatically improve the yield, which will be disclosed in this paper.

First investigation of the Diels–Alder reaction of cyclopentadiene (CP) and benzyl acrylate in $CHCl_3$ was carried out using a Beckman L-60 Ultracentrifuge fitted with a SW55Ti swinging bucket rotor centrifuged at 40,000 rpm (285,000 g) at 23 °C for 50 min.[7] As expected from the results of Bergman, only a slight increase of the rate acceleration was observed: That is, 73% yield was obtained under ultracentrifugation in comparison of 67% under ambient pressure (Table 1, Entries 2 and 7).

The pressure should vary over the length of the tube. That is, at the top of the tube, ambient pressure would be expected, while high pressure should be achieved at the bottom. To utilize the high pressure induced by centrifugation effectively, a two-phase system, in which upper and lower phases were respectively aqueous and organic, was employed. Using this method, organic reactions could be performed under high pressure. To realize this scenario, $CHCl_3$ was used as the organic solvent because of its large specific gravity[8] and the two-phase reaction was set-up to be performed as follows: $CHCl_3$ (90 µL), freshly distilled CP (86 µL, 1.0 mmol), and benzyl acrylate (70 µL, 0.43 mmol) were mixed in a tube, and a certain amount of water was gently placed on the top of the organic phase. The tube was placed in the ultracentrifuge and the remainder of the experiment was performed as described above.



The amount of water had a great effect on the yield under ultracentrifugation conditions, but none under ambient pressure. Under ultracentrifugation, the yield increases along with an increasing volume of water. That is, when the volume of water was 0, 1, 2, and 3 mL, the yields were 73, 78, 86, and 91%, respectively (Entries 2–5). Under ambient pressure, however, the volume of water did not affect the yield at all (Entries 7 and 8). The endo/exo selectivity is hardly affected either by centrifugation or the amount of water.



(1)

Table 1. Diels–Alder reaction of benzyl acrylate with CP under centrifuged reaction conditions (40,000 rpm) and ambient pressure

Entry	Method[a]	Amount of $CHCl_3$/µL	Amount of H_2O/mL	Yield/%[b]	endo:exo[c]
1	A	0	0	81	80:20
2	A	90	0	73	79:21
3	A	90	1	78	82:18
4	A	90	2	86	82:18
5	A	90	3	91	81:19
6	B	0	0	73	78:22
7	B	90	0	67	79:21
8	B	90	3	66	80:20

[a]The reaction was performed using of 70 µL (0.43 mmol) of benzyl acrylate and 86 µL (1.0 mmol) of CP under centrifugation conditions (Method A) or under ambient conditions (Method B). [b]Yield of isolated product. [c]The ratio (endo:exo) was determined by ^1H NMR analysis (400 MHz).

As the pressure is a function of the sequence of rotation speed, the acceleration of the reaction would be expected when reaction is carried out under high rotation speed. The reaction was performed in 6.5-mL-sample tube using benzyl acrylate

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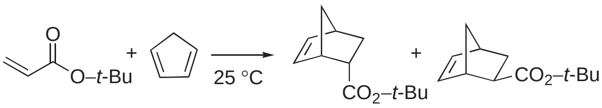
Table 2. Diels–Alder reaction of benzyl acrylate with CP under centrifuged reaction conditions (100,000 rpm) and ambient pressure

Entry	Method[a]	Time/min	Yield/%[b]	endo:exo[c]
1	A	10	53	83:17
2	A	20	68	82:18
3	A	50	87	81:19
4	B	10	9	79:21
5	B	20	19	79:21
6	B	50	29	80:20

[a]The reaction was performed using of 70 µL (0.43 mmol) of benzyl acrylate, 86 µL (1.0 mmol) of CP, $CHCl_3$ 110 µL and water 6 mL under centrifugation conditions (Method A) or under ambient conditions (Method B). [b]Yield of isolated product. [c]The ratio (endo:exo) was determined by ^1H NMR analysis (400 MHz).



(2)

Table 3. Diels–Alder reaction of *tert*-butyl acrylate with CP under centrifuged reaction conditions (100,000 rpm) and ambient pressure

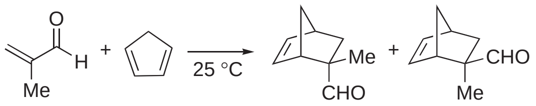
Entry	Method[a]	Time/min	Yield/%[b]	endo:exo[c]
1	A	20	60	82:18
2	A	50	82	79:21
3	B	20	20	79:21
4	B	50	29	84:16

[a]The reaction was performed using 70 µL (0.80 mmol) of *tert*-butyl acrylate, 160 µL (1.9 mmol) of CP, $CHCl_3$ 110 µL and water 6 mL under centrifugation conditions at 100,000 rpm (Method A) or under ambient conditions (Method B). [b]Yield of isolated product. [c]The ratio (endo:exo) was determined by ^1H NMR analysis (400 MHz).

(70 µL), CP (86 µL), $CHCl_3$ (110 µL), and water (6.0 mL) by the use of HITACHI CP100MX Preparative Ultracentrifuge with P100AT2 fixed angle rotor with 100,000 rpm (803,000 g),[7] in which the calculated pressures at the top and bottom of the organic phase are 1752 and 2050 atm respectively. The results summarized in Table 2 indicate the large acceleration under ultracentrifugation, affording the product in good yield (87%) after 50 min, in comparison to the low yield (29%) at ambient pressure.

As the good results are obtained, this ultracentrifugation-mediated high-pressure reaction was applied to other Diels–Alder reactions, those of CP with *tert*-butyl acrylate (Table 3), and with methacrolein (Table 4). The same phenomena were observed for both reactions as for the reaction with benzyl acrylate; namely, the reaction is accelerated under ultracentrifugation conditions with a two-phase system in comparison with the reaction at ambient pressure.

It is well known that the Diels–Alder reaction is accelerated in water owing to the hydrophobic effect.[9,10] In the present Diels–Alder reaction, the reaction proceeds smoothly with no stirring at all, maintaining the two-phase reaction conditions throughout the course of the reaction. Thus, the acceleration of the reaction cannot be attributed to the well-known hydrophobic effect, but rather to another cause. That is, the water acts like a weight exerting a high pressure on the lower-organic phase.



(3)

Table 4. Diels–Alder reaction of methacrolein with CP under centrifuged reaction conditions (100,000 rpm) and ambient pressure

Entry	Method[a]	Time/min	Yield/%[b]	endo:exo[c]
1	A	20	37	19:81
2	A	50	68	17:83
3	B	8	8	33:67
4	B	50	15	22:78

[a]The reaction was performed by using 70 µL (0.85 mmol) of methacrolein, 280 µL (3.4 mmol) of CP $CHCl_3$ 140 µL and water 6 mL under centrifugation conditions at 100,000 rpm (Method A) or under ambient conditions (Method B). [b]Yield of isolated product. [c]The ratio (endo:exo) was determined by ^1H NMR analysis (400 MHz).

In summary, this paper describes the successful application of ultracentrifugation, a technique widely used in biochemistry and biology laboratories, to the Diels–Alder reaction by using a two-phase reaction system. As it is known that many organic reactions are accelerated under high pressure, the present high-pressure technique involving the combined use of centrifugation and a two-phase reaction system will provide a useful and unique method for organic synthesis.

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This paper is dedicated to Professor Teruaki Mukaiyama on the occasion of his 80th birthday.

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