modest and definable differences in membrane composition and packing can lead to large differences in lability, and that synthetic agents can be created which exploit such differences. They also reveal the fact that subtle changes in surfactant structure can result in dramatically different interactions with lipid bilayers.

Finally, it should be mentioned that the ability of a microorganism to develop resistance toward a drug that functions via membrane disruption is likely to be less than one which operates at the nuclear or cytoplasmic level. In principle, therefore, membrane-disrupting antimicrobial agents may be better suited for treating those diseases that require long-term administration (e.g., AIDS). It is noteworthy, in this regard, that recent in vitro studies have shown that the human bacterium mycoplasma *M. fermentans* can profoundly enhance the cytotoxicity of HIV-1 toward CD4$^+$ human T-lymphocytes.[23] If such synergy is found to exist in vivo, then the synthesis of membrane-disrupting anti-mycoplasma agents could represent a rational approach toward novel anti-AIDS drugs.[24]

A detailed kinetic and mechanistic investigation into the membrane-disrupting action of I–VI, as well as the design and synthesis of second-generation analogues, is now in progress. The results of these studies will be reported in due course.

Acknowledgment. We are grateful to Dr. Ferenc J. Kezdy (Upjohn Co.) for many valuable discussions and to Mr. Wally Patton (Lehigh) for technical assistance.

(23) Lo, S.-C.; Tsai, S.; Benish, J. R.; Shih, J. W.-K.; Wear, D. J.; Wong, D. M. *Science* **1991**, *251*, 1074.

(24) In preliminary studies, II has been found to completely inhibit the growth of two human strains of mycoplasma fermentans (i.e., Incognitus and PG18) at a concentration level of 63 μg/mL; complete inhibition by I required a concentration of 1000 μg/mL: Lo, S.-C.; Kotani, H.; Regen, S. L. Unpublished results. Thus, the greater anti-mycloplasma activity observed with the supramolecular surfactant correlates with its higher activity in disrupting fluid POPC bilayers.

Oxidative α Coupling of Carbonyl Compounds via the Condensation of Acylated Triazolinedione Ylides with Enolates: A Facile Synthesis of Polyacylated Olefins

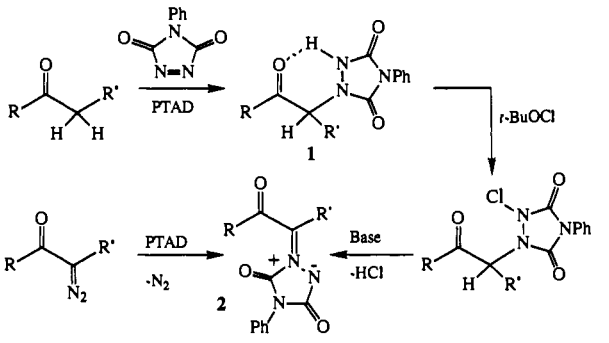
R. Marshall Wilson,* Alvan C. Hengge, Ali Ataei, and Douglas M. Ho

Contribution from the Department of Chemistry, University of Cincinnati, Cincinnati, Ohio 45221-0172. *Received October 11, 1990. Revised Manuscript Received April 11, 1991*

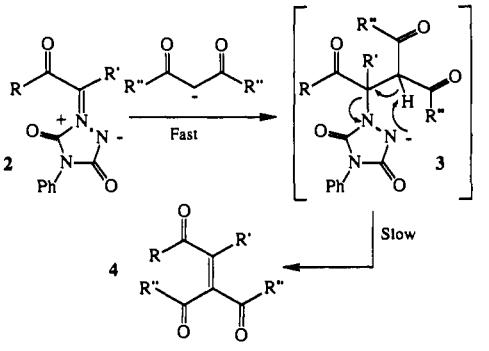
Abstract: α-Urazolyl ketones are readily oxidized to acylated *N*-phenyltriazolinedione ylides with *tert*-butyl hypochlorite. These ylides, usually as generated in situ, undergo condensations with enolate species to form acylated olefins in synthetically useful yields. The ylide derived from deoxybenzoin is sufficiently stable to be isolated and characterized, and displays the same type of condensation chemistry with enolates as do other less stable ylides that must be generated in situ. The tri- and tetraacylolefins produced by this method are susceptible to subsequent Michael addition of enolates. Intramolecular cyclization or basic cleavage of these Michael adducts leads to a variety of interesting secondary products.

N-Phenyltriazolinedione (PTAD) ylides constitute a relatively obscure class of reactive intermediates which have recently been shown to undergo extremely facile condensations with a variety of nucleophiles.[1] More recent efforts have shown that ylide precursors, α-urazolylcarbonyl compounds (**1** in Scheme I), are readily available through the reaction of a wide variety of carbonyl compounds with PTAD.[2] In an effort to extend the scope of this novel condensation chemistry of PTAD ylides, we have investigated the generation of acylated PTAD ylides (**2**) from these α-urazolylcarbonyl compounds,[3] and in this paper we report the condensation chemistry of these acylated ylides with a variety of enolate species as outlined in Scheme II and Table I.

Scheme I



Scheme II



PTAD Ylides and Their Reactions with Enolates

In a number of instances, PTAD ylides may be isolated as moderately stable, colored solids.[1,4,5] As might be expected, these more stable ylides all contain stabilizing electron-donating or phenyl substituents. In the ylides under study here, the electron-withdrawing acyl substituent tends to destabilize the ylides to the extent that they cannot be isolated unless they are stabilized by a complementary electron-donating substituent such as a phenyl group (**2**, R′ = Ph).[4] Thus, in most of the condensation reactions studied here (Table I), the ylides were not isolated, but were prepared in situ. The α-urazolylcarbonyl compounds were oxidized

(1) (a) Wilson, R. M.; Hengge, A. C. *Tetrahedron Lett.* **1985**, *26*, 3673. (b) Wilson, R. M.; Hengge, A. C. *J. Org. Chem.* **1987**, *52*, 2699.
(2) Wilson, R. M.; Hengge, A. C.; Ataei, A.; Chantarasiri, N. *J. Org. Chem.* **1990**, *55*, 193.
(3) Wilson, R. M.; Hengge, A. C. *J. Org. Chem.* **1990**, *55*, 197.
(4) Theis, W.; Bethäuser, W.; Regitz, M. *Tetrahedron* **1985**, *41*, 1965. Theis, W.; Bethäuser, W.; Regitz, M. *Chem. Ber.* **1985**, *118*, 28.
(5) Wilson, R. M.; Chantarasiri, N. *J. Am. Chem. Soc.* **1991**, *113*, 2301.

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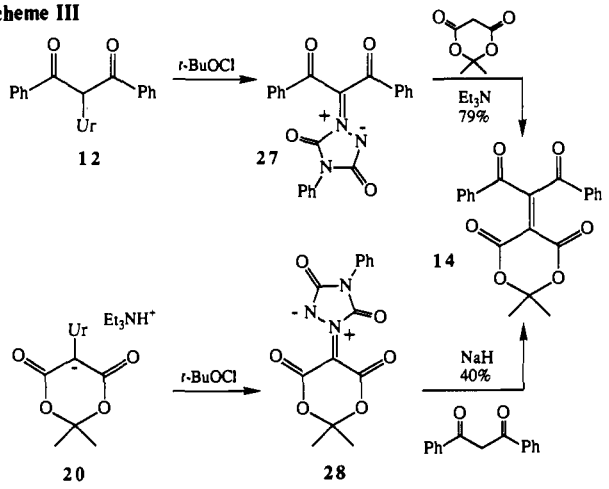
Scheme III



to the *N*-chlorourazoles or the corresponding ylides and immediately treated with the enolate species. Under these conditions, the characteristic ylide color forms immediately upon oxidation of **1** and is bleached immediately upon addition of the enolate species. This rapid bleaching corresponds to the addition of the enolate to the ylide **2** to form the adduct **3** as shown in Scheme II. Adduct **3** in turn slowly undergoes the elimination of *N*-phenylurazole to form the final olefin product **4**. This sequence of mechanistic events is supported by the fact that only poor yields of the olefin products **4** can be obtained if isolation is attempted immediately after the ylide color is bleached. Much better olefin yields are realized if the bleached reaction mixture is allowed to stand for several hours or days at room temperature or even heated briefly. Furthermore, the condensation yields can be improved significantly by preparing the PTAD ylide via the diazoketone route shown in Scheme I and using the isolated ylide in condensation reactions rather than preparing the ylide in situ (compare entries 2 and 3 in Table I). Unfortunately, of the ylides studied in this work, only the ylide **5** was stable enough to be isolated, and so all other condensations investigated here utilized ylides generated in situ.

As can be seen from the examples listed in Table I, this overall process for coupling two carbonyl components leads to olefins with various degrees of acylation. In general, three coupling strategies are available. Strategy I provides diacylolefins through the oxidative coupling of two simple ketones. The symmetrical coupling of deoxybenzoin via the stable ylide **5**[4] affords the diacylated olefins **6**[6] and **7**[7] (Table I, entry 1). Strategy II affords triacylolefins through the coupling of simple ketones with 1,3-dicarbonyl compounds. Thus, condensation of either the ylide **5**[4] or the ylide derived from urazolyl ketone **9**[2] with Meldrum's acid, dimedone, and dimethyl malonate affords the triacylated olefins **8**, **10**, and **11**, respectively (Table I, entries 2–5). Finally, strategy III provides access to unusual tetraacylolefins through the coupling of two 1,3-dicarbonyl compounds. Examples of this strategy for the preparation of symmetrical tetraacylolefins are the coupling of the urazole derivative of dibenzoylmethane **12** with dibenzoylmethane to form the tetrabenzoylethylene (**13**)[8] (Table I, entry 6), and the urazole derivative of Meldrum's acid **20** with Meldrum's acid to form the symmetrical Meldrum's acid coupling product **21** (Table I, entry 11).

Examples of this type of coupling to form unsymmetrical tetraacylolefins have also been investigated. Of course all such unsymmetrical couplings can be achieved by either of two routes as illustrated for the formation **14** in Scheme III (Table I, entries 7 and 12). At least in this one example, the route proceeding through the diketone ylide **27** is nearly twice as effective as the route proceeding through the diester ylide **28**. In general, the more

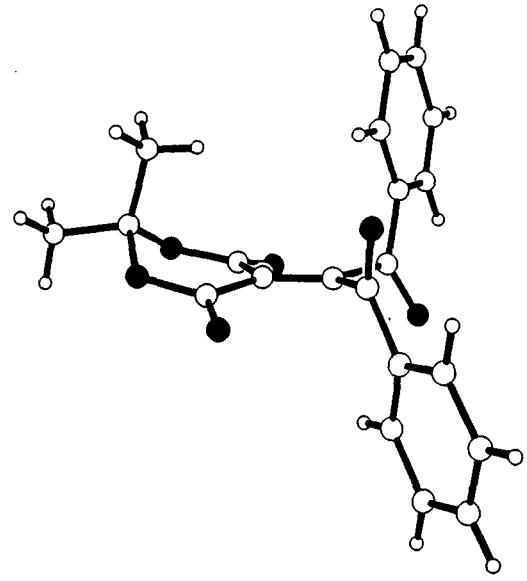
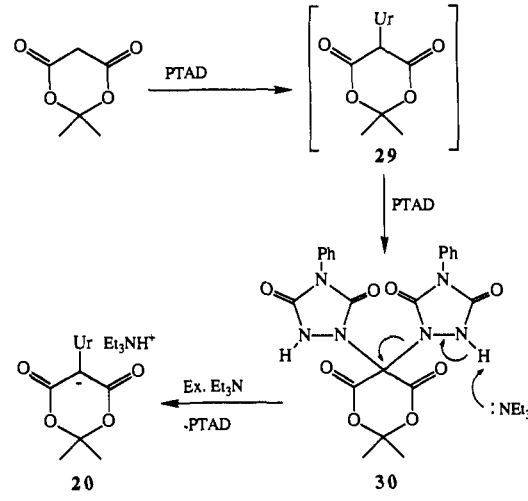


Figure 1. X-ray crystal structure of the coupling product of 1,3-diphenyl-1,3-propanedione and Meldrum's acid **14**. ○ = carbon, and ● = oxygen.

Scheme IV



efficient route seems to be the one proceeding through the more stable, longer lived ylide. A further consideration in choosing between two such alternative routes is the availability of the precursor urazoles. In the example shown in Scheme III, the urazole **12** is readily available in 85% yield from the reaction of PTAD with the parent diketone.[2] In contrast, urazole **20** is only available through a rather circuitous route. Reaction of Meldrum's acid with PTAD does not afford isolable quantities of the monourazole adduct **29** (Scheme IV), but yields the bis(urazole) adduct **30** in 53% yield instead.[2] However, the monourazole adduct in the form of its triethylamine salt **20** can be obtained in excellent yield (92%) through a unique deurazolation of the bis(urazole) adduct **30** as shown in Scheme IV. Apparently under these conditions, the released PTAD reacts with the excess triethylamine. The structure of this unusual Meldrum's acid salt **20** has been confirmed by X-ray crystallography.[9]

In order to reinforce the structure assignments of these spectroscopically rather uninformative polyacylated olefins, an X-ray crystallographic study of the tetraacylated olefin **14** was also conducted. The results of this study are summarized in Figure 1.[9] From these X-ray data it was determined that the central carbon–carbon double bond was unexceptional with a bond length of 1.340 Å. However, it is interesting to note that, at least in the crystal, the π-systems of the two benzoyl groups are essentially

(6) Lutz, R. E.; Baver, C. R.; Lutz, R. C.; Gillespie, J. S. *J. Org. Chem.* **1955**, *20*, 218.
(7) Foote, C. S.; Wexler, A.; Ando, W. *J. Am. Chem. Soc.* **1968**, *90*, 975.
(8) Cava, M. P.; Behforouz, M.; Husbands, G. E. M.; Srinivason, M. J. *J. Am. Chem. Soc.* **1973**, *95*, 2561.

(9) For detailed X-ray crystallographic data for compounds **14**, **17**, **20**, and **26**, see the paragraph about supplementary material at the end of this paper.

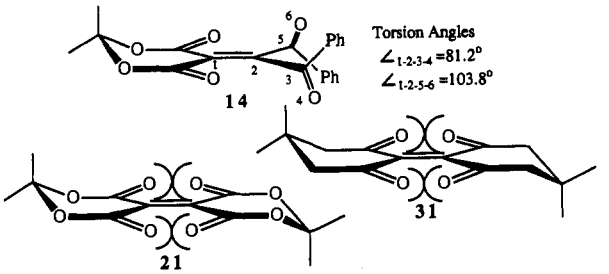
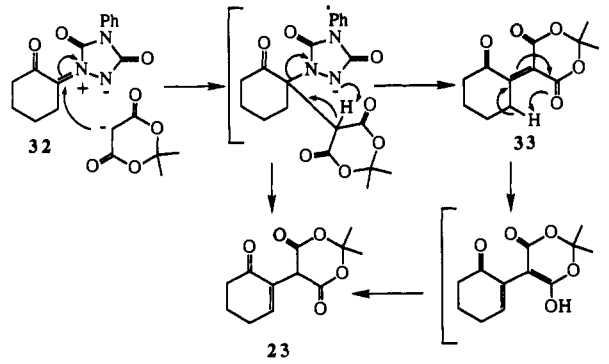


Figure 2. Conformations of the tetraacylolefins **14**, **21**, and **31**.

Scheme V



orthogonal to the π-system of the central carbon–carbon double bond.

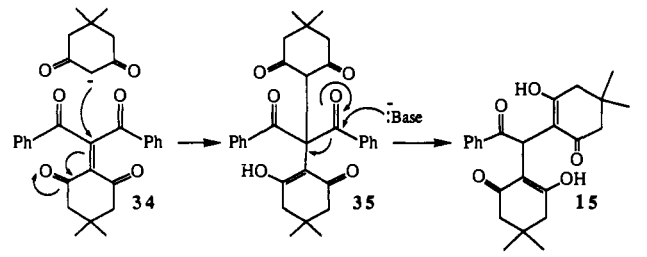
Chemistry of Tri- and Tetraacylolefins

The polyacylated olefins produced in these reactions can be extremely reactive substances. There seems to be a tendency for those olefins derived from cyclic ketones and cyclic 1,3-diketones to be more reactive than those derived from acyclic analogues. This reactivity pattern is probably governed by the rotational freedom of the carbonyl groups. Thus, an X-ray crystal structure of **14** clearly shows that the two carbonyl groups derived from the dibenzoylmethane moiety have rotated so as to be almost completely out of conjugation with the central carbon–carbon double bond (Figures 1 and 2). On the other hand, the two carbonyl groups of the Meldrum's acid moiety are forced by the 1,3-dioxane ring to be coplanar with, and hence, conjugated with the central carbon–carbon double bond. In contrast all four carbonyl groups of the oxidative coupling product of Meldrum's acid **21** are forced to be essentially coplanar with the central double bond. Presumably the same type of enforced coplanarity is present in the oxidative coupling product (**31**) of dimedone.

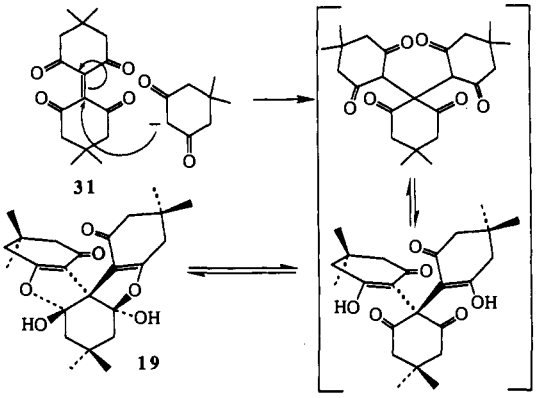
This type of ring-enforced coplanarity probably enhances the reactivity of polycarbonyl systems in several ways. The overlap of the π-orbitals of all four carbonyl groups with that of the central carbon–carbon double bond should greatly enhance the electron deficiency of this central double bond. Thus, this central double bond should serve as a powerful electrophile and be much more susceptible to attack by enolates in Michael addition reactions. Furthermore, the steric congestion between the syn carbonyl groups in tri- and tetracoplanar systems such as **21** and **31**, as shown in Figure 2, should provide a source of steric strain. Consequently, attack of nucleophiles upon the central double bond or any other reaction that destroys the coplanarity of the carbonyl groups would relieve this steric congestion and provide an additional driving force for reaction. These factors are of considerable value in rationalizing the tendency of tri- and tetraacylolefins to undergo reaction at the central double bond.

For example, in the reaction of the cyclohexanone ylide **32** with Meldrum's acid (Scheme V), the coupling product **23** is the only relatively nonpolar product isolated (Table I, entry 13). Apparently, the initially formed triacylolefin **33** undergoes double-bond migration as a means of relieving the steric strain imposed by the planarity of the initially formed tetrasubstituted double bond. This might occur via an intramolecular enolization as

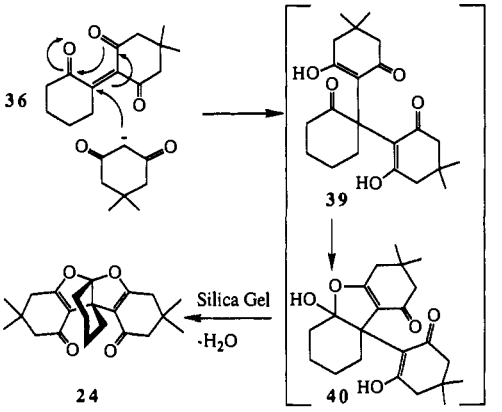
Scheme VI



Scheme VII



Scheme VIII



indicated in Scheme V, or perhaps less likely, urazole elimination might occur to afford **23** directly.

Furthermore, in most of the condensations with dimedone, secondary reaction products predominate (Table I, entries 8, 10, 14, and 15). These secondary reactions are all initiated by Michael additions of the dimedone enolate to the highly reactive central double bonds of the primary coupling products, **34**, **31**, and **36** in Schemes VI, VII, and VIII, respectively. In the case of the tetraacylolefin **34** in Scheme VI, cleavage of the nonenolizable 1,3-diketone unit in **35** leads to the bis(dimedone) adduct of acetophenone (**15**, Table I, entry 8). Alternatively, in the case of the symmetrical dimedone coupling product **31** in Schemes VII, Michael addition of a third dimedone unit and subsequent intramolecular ketal formation leads to the observed product **19** (Table I, entry 10). Related bis(dimedone) adducts are formed in the reactions of dimedone with the cyclohexanone–dimedone coupling product **36** (Scheme VIII, Table I, entry 14) and with the oxindole–dimedone coupling product derived from urazole **25** (Table I, entry 15).

The structures of the bis(dimedone) adducts **19**, **24**, and **26** are rather complex and their assignments require some discussion. The structure of bis adduct **26** (Table I, entry 15) is the most firmly established and is based upon an X-ray crystal study (Figure 3).[9] As can be readily seen in Figure 3, the stereochemistry of **26** probably is governed by the intramolecular hydrogen bonding between the hemiketal –OH and the oxindole carbonyl group. This

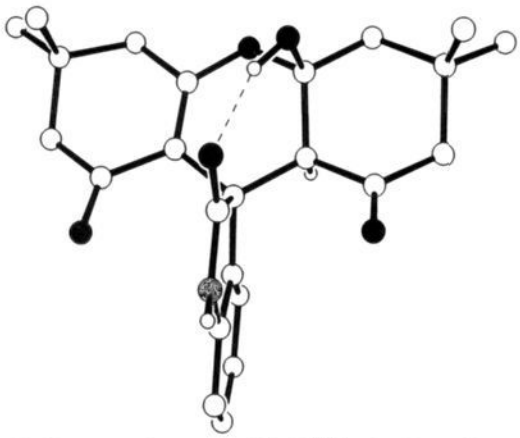


Figure 3. X-ray crystal structure of the bis(dimedone) coupling product of oxindole **26**. ○ = carbon, ● = oxygen, and ◎ = nitrogen.

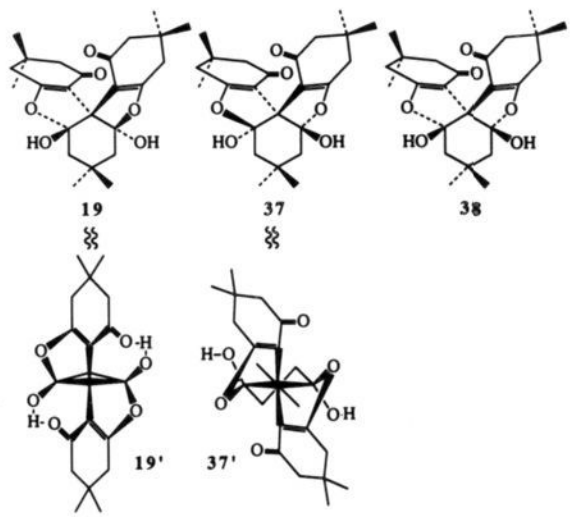


Figure 4. Isomers **19**, **37**, and **38** of the bis(dimedone) coupling product of dimedone. Projections **19′** and **37′** illustrate how intramolecular hydrogen bonding might occur in isomer **19**, but not in isomer **37**.

hydrogen bonding will stabilize the cis configuration between these two groups relative to the trans configuration, and probably will determine the stereochemistry of the ring fusion of the cyclohexanone ring as well.

The trimeric dimedone coupling product **19** (Table I, entry 10) displays a high degree of symmetry in its NMR spectra. The ^{1}H NMR spectrum displays three methyl singlets and three pairs of coupled doublets with each doublet corresponding to two hydrogens (see the Experimental Section). The ^{13}C NMR spectrum displays three triplets in the aliphatic region and four singlets above 100 ppm. These data are consistent with a molecule having C_2 symmetry. Of the three most probable bis adduct isomers, **19**, **37**, and **38**, only **38** does not have C_2 symmetry (Figure 4). Furthermore, while both **19** and **37** do have C_2 symmetry, only **19** has a stereochemistry suitable for intramolecular hydrogen bonding as illustrated in projections **19′** and **37′**.

Since the hemiketal units of **19**, **37**, and **38** all would be expected to undergo equilibria with the open ketone forms, all three of these isomers should be in equilibrium with each other. Under these circumstances, the generation of the less strained *cis*-dihydrofuran ring fusions and the associated intramolecular hydrogen bonds should favor formation of **19** over **37** and **38**.[10] This same type

(10) Molecular modeling studies (Biosym, Insight II, Version 1.0.2, Biosym Technologies, 10065 Barnes Canyon Road, San Diego, CA 92121) indicate that of the three isomers in Figure 4, **19** is the most stable, and that the *trans-fused dihydrofuran rings add considerable strain to the molecule.* Further, **19** displays facile intramolecular hydrogen bonding with hydrogen bond lengths of about 1.70 Å.

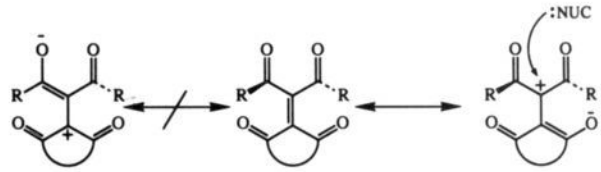
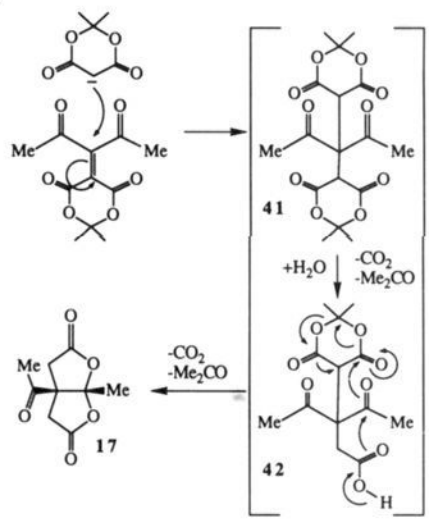


Figure 5. Polarization of the central double bond of unsymmetrical tetraacyclolefins induced by twisting of the carbonyl groups at the acyclic terminus.

Scheme IX



of intramolecular hydrogen bonding apparently contributes to the stabilization of **26** over other possible isomers of this oxindole system.

The bis(dimedone) coupling product of cyclohexanone **24** (Table I, entry 14) also displays highly symmetric NMR spectra. This is particularly evident in the ^{13}C NMR spectrum, which displays four triplets associated with the cyclohexanone residue and two triplets associated with the two dimedone residues. In addition, singlets associated with a ketal carbon atom (δ 116.9 ppm), a diallylic carbon atom (δ 55.3 ppm), and two equivalent *gem*-dimethyl-bearing carbon atoms (δ 33.7 ppm) complete the spectrum. This spectrum is consistent with a molecule having a plane of symmetry in which all of the cyclohexanone-derived carbons, including the ketal carbon, are on the plane of symmetry and the two dimedone residues are symmetrically disposed on either side of the plane. Furthermore, in the crude reaction mixture, two products are present, **24** and another unstable material that upon exposure to silica gel is converted rapidly to **24**. These data are in accord with the final, symmetrical ketal product having structure **24** (Scheme VIII), and the unstable intermediate being either the keto or hemiketal forms **39** or **40**, respectively. Apparently silica gel serves as an effective dehydrating agent in the final cyclization of the hemiketal **40** to **24**.

A final variation on the secondary reactions of tetraacylolefins is shown in Scheme IX (Table I, entry 9). In this case, partial hydrolysis and decarboxylation of the bis(Meldrum's acid) coupling product **41** would lead to the monocarboxylic acid derivative **42**. Bicyclization of **42** with cleavage of the second Meldrum's acid unit would afford the acylal **17**. An X-ray crystallographic study of **17** has confirmed the structure of this novel substance and established the cis stereochemistry of the ring fusion between the lactone rings.

It should be noted that in the examples cited above involving unsymmetrical tetraacylolefins, Schemes VI and IX, the secondary Michael additions occur with attack of the enolate nucleophile at the central double bond terminus bearing the acyclic unit as indicated in Figure 5. This regiochemistry probably is determined by the twisting of the carbonyl groups at the acyclic terminus out of conjugation with the central double bond (Figures 1 and 2). This twisting would polarize the central double bond toward the

Table I. Condensations of PTAD Ylides with Enolates: Reaction Conditions, Products, and Yields

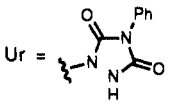
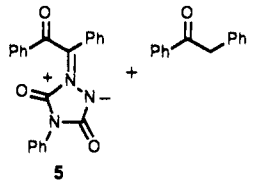
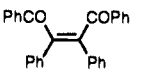
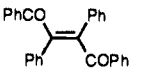
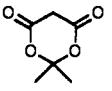
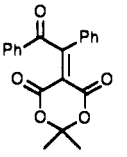
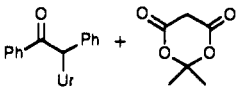
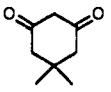
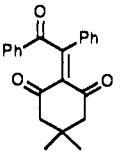
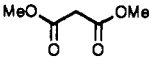
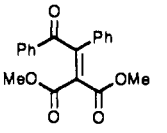
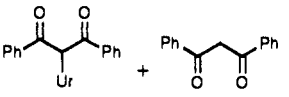
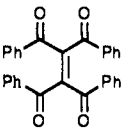
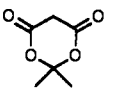
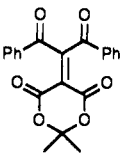
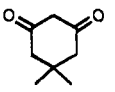
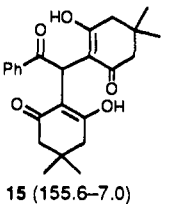
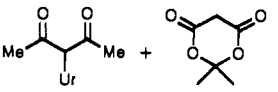
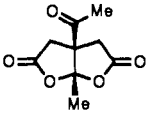
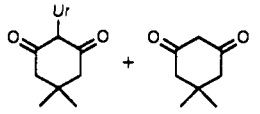
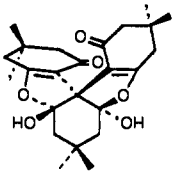
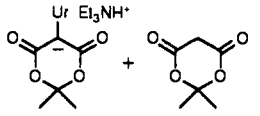
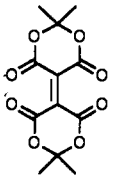
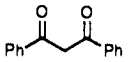
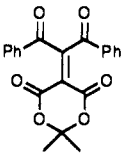
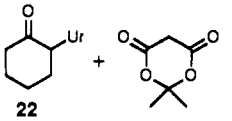
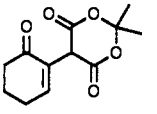
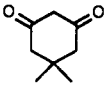
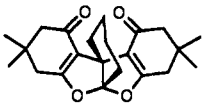
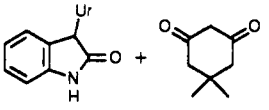
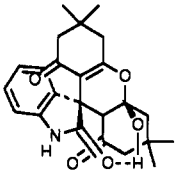
entry	starting materials	reaction conditions[a]	products (mp, °C)	yields, %
	Ur = 			
1	 **5**	(1) *t*-BuOK, THF, 0 °C (30 min) (2) **5**, 0 °C (1 h), rt (4 days)	 **6** (216–7[b])  **7** (228.0–9.5[d])	57[c] (**6**:**7** = 80:20)
2	**5** + 	(1) Et_3N, THF (30 min) (2) **5**, 0 °C (1 h), rt (3 days)	 **8** (197.0–8.5)	61[c]
3	 **9**	(1) Et_3N, DMF, 0 °C (15 min) (2) **9**, *t*-BuOCl, DMF, rt (3) (1) + (2), rt (12 h)	**8** (197–8)	50
4	**9** + 	(1) Et_3N, DMF, 0 °C (15 min) (2) **9**, *t*-BuOCl, DMF, rt (3) (1) + (2), rt (5 h)	 **10** (153.6–5.0)	58
5	**9** + 	(1) NaH, DMF, 0 °C, (20 min) (2) **9**, *t*-BuOCl, DMF (3) (1) + (2), −40 °C to rt (14 h)	 **11** (120.0–0.7)	64
6	 **12**	(1) NaH, THF, rt (30 min) (2) **12**, *t*-BuOCl, THF (1 min) (3) (1) + (2), rt (2 days)	 **13** (185.5–6.5)	12
7	**12** + 	(1) Et_3N, DMF, 0 °C (30 min) (2) **12**, *t*-BuOCl, THF (1 min) (3) (1) + (2), 0 °C (1 h) to rt (7 h)	 **14**[e] (200 dec)	79
8	**12** + 	(1) Et_3N, DMF, 0 °C (25 min) (2) **12**, *t*-BuOCl, THF (3) (1) + (2), 0 °C to rt (12 h)	 **15** (155.6–7.0)	47
9	 **16**	(1) Et_3N, CH_3CN, 0 °C (30 min) (2) **16**, *t*-BuOCl, CH_3CN (3) (1) + (2), rt (5 h)	 **17**[e] (192.0–2.5)	69

Table I (Continued)

entry	starting materials	reaction conditions[a]	products (mp, °C)	yields, %
10	 **18**	(1) Et_3N, CH_3CN, 0 °C (30 min) (2) **18**, *t*-BuOCl, CH_3CN (3) (1) + (2), rt (18 h)	 **19** (201–3)	55
11	 **20**[e]	(1) Et_3N, DMF, 0 °C (30 min) (2) **20**, *t*-BuOCl, DMF (3) (1) + (2), rt (12 h)	 **21** (210 dec[f])	7
12	**20**[e] + 	(1) NaH, CH_3CN, 0 °C (30 min) (2) **20**, *t*-BuOCl, CH_3CN (3) (1) + (2), rt (18 h)	 **14**[e] (200 dec)	40
13	 **22**	(1) Et_3N, CH_3CN, rt (20 min) (2) **22**, *t*-BuOCl, CH_3CN (3) (1) + (2), rt (12 h)	 **23** (151.0–2.3)	58
14	**22** + 	(1) Et_3N, DMF, 0 °C (20 min) (2) **22**, *t*-BuOCl, DMF (3 min) (3) (1) + (2), 0 °C to rt (14 h) silica gel chromatography	 **24** (132.9–3.7)	71
15	 **25**	(1) Et_3N, DMF, 0 °C (15 min) (2) **25**, *t*-BuOCl, DMF, 0 °C (3) (1) + (2), 0 °C to rt (12 h)	 **26**[e] (237 dec)	92

[a] (1) The conditions for enolate formation, (2) the conditions for ylide formation, except in entries 1 and 2 where the ylide is preformed, and (3) the conditions for reaction between enolate and ylide, including elimination of 4-phenylurazole. [b] Reference 6. [c] Yield based on PTAD ylide. [d] Reference 7. [e] Structure determined by X-ray crystallography; see ref 9. [f] Reference 15.

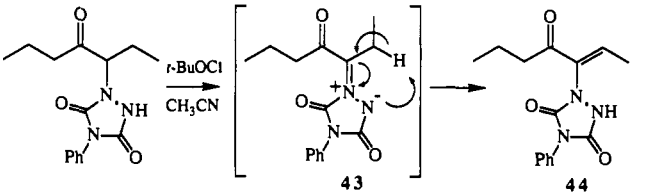
cyclic dicarbonyl unit and direct the attacking nucleophile toward the acyclic terminus.

Alternative Modes of PTAD Ylide Reaction

Finally, the observation of several alternative modes of ylide chemistry do indicate possible limitations of this methodology for the synthesis of olefins via carbonyl coupling. Thus for example, even though the PTAD ylide derived from α-urazolylcyclohexanone (**22**) is sufficiently long-lived to permit its reaction with enolates, the ylides derived from some other aliphatic ketones do not undergo appreciable reaction with enolates under similar conditions. The ylide derived from 4-heptanone, **43**, is one of these. Instead of affording condensation products with enolates, **43** apparently undergoes rapid ylide annihilation via intramolecular proton abstraction to form the vinyl urazole **44** as outlined in Scheme X.[3] This same type of ylide annihilation also has been observed with the ylide derived from cyclooctanone.

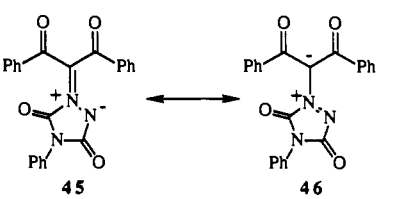
Furthermore, if one considers the two possible ylide resonance structures **45** and **46**, one might come to the conclusion that resonance structure **46** would be the major contributor for acyl-substituted ylides, and hence should play a major role in the chemistry of the ylides described in this paper. This does not seem to be the case when the attacking nucleophiles are enolates. Thus the only products of the reaction of enolates are those arising from

Scheme X



43 **44**

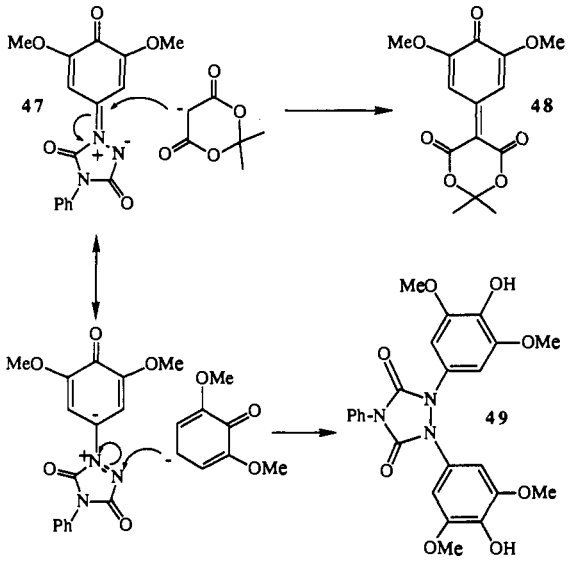
the nucleophilic attack on the ylide carbon atom, which is apparently governed by resonance structures related to **45**. However,



45 **46**

other related PTAD ylides do exhibit ambiphilic behavior.[5] Thus, the dienone PTAD ylide **47** illustrated in Scheme XI will undergo attack by nucleophiles at either the ylide carbon atom to form olefins such as **48**, or the terminal ylide nitrogen atom to afford

Scheme XI



N,N'-disubstituted urazoles such as **49**. This latter mode of nucleophilic attack on the terminal ylide nitrogen atom seems to be dependent on the structure of the nucleophile, and has not been observed with simple enolates to date.

Conclusions

This new condensation of carbonyl compounds with α-acyl PTAD ylides provides a most convenient method for the oxidative coupling of carbonyl compounds and for the rapid synthesis of highly reactive, polyacylated olefins. Indeed the polyacylated olefins that are formed in these ylide condensations are so reactive that they frequently undergo subsequent Michael additions of the same enolate that participated in the original ylide condensation. These secondary reactions lead to novel bis coupling products that are themselves quite reactive and undergo a variety of further transformations leading to quite complex ring systems.

Experimental Section

Melting points were determined with a Mettler FP2 melting point apparatus with a polarizing microscope and are uncorrected. ^1H and ^{13}C NMR spectra were recorded with either an IBM NR-80 MHz or a Nicolet NT-300 MHz spectrometer. Spectra were recorded in $CDCl_3$ except where noted otherwise, and chemical shifts are reported in ppm downfield from tetramethylsilane as an internal standard. Infrared spectra were recorded on a Perkin-Elmer 599 infrared spectrometer and were calibrated with a polystyrene film. High-resolution mass spectra were obtained with a Kratos MS801-DS55 spectrometer. UV–vis spectra were recorded with a Perkin-Elmer Lambda 5 spectrometer.

Analytical thin-layer chromatography was conducted by using E. Merck silica gel 60-PF254 precoated plates. Compounds were visualized by UV light (254 nm) and by I_2 vapor. Preparative chromatographic separations were conducted by centrifugal chromatography with a Chromatotron on plates coated with E. Merck silica gel 60-PF254, or by column chromatography using Fisher neutral alumina, 80–200 mesh. For flash chromagoraphic separations, E. Merck silica gel 60, 230–400 mesh, was used.

Solvents and reagents were used as received unless otherwise noted. Tetrahydrofuran was freshly distilled from benzophenone ketyl. Acetonitrile and DMF were distilled from barium oxide and stored over molecular sieves. Dimethoxyethane was distilled from lithium aluminum hydride and stored over molecular sieves. Triethylamine was distilled from lithium aluminum hydride and stored over KOH. Benzene was dried over sodium ribbon. *tert*-Butyl hypochlorite was prepared by the literature method[11] and stored over calcium chloride. Meldrum's acid was prepared by the literature method.[12] PTAD was prepared by a modification of the standard *tert*-butyl hypochlorite method.[1b,13] All reactions were conducted under an atmosphere of either nitrogen or argon in oven-dried or flame-dried glassware. All extracts were dried over $MgSO_4$.

Preparation of the 3,5-Dioxo-2-(2-oxo-1,2-diphenylethylidene)-4-phenyl-1,2,4-triazolidine Ylide (5). A solution of PTAD (39.4 mg, 0.225 mmol) in 2 mL of benzene was added dropwise to a solution of phenylbenzoyldiazomethane[14] (49.95 mg, 0.225 mmol) in 1 mL of benzene. After 10 min, the solvent was removed by evaporation and the residue triturated with 10 mL of ether. The yellow precipitate was removed by filtration, and the filtrate was evaporated to dryness again and triturated with another 10-mL portion of ether to afford two crops of **5** as a yellow-orange powder (59.0 mg, 71%), mp 160 °C dec (lit.[4] mp 170 °C dec).

Reaction of the Ylide 5 with Deoxybenzoin. Preparation of *cis*- and *trans*-Dibenzoylstilbene (6 and 7, Respectively). A solution of deoxybenzoin (13.3 mg, 0.068 mmol) and potassium *tert*-butoxide (7.6 mg, 0.068 mmol) in 4 mL of THF at 0 °C was stirred for 30 min. A separate solution of **5** (25.0 mg, 0.068 mmol) in 3 mL of THF was immediately added to the enolate solution. The resulting mixture was stirred for 1 h at 0 °C and at room temperature for 4 days. The reaction mixture was poured into an ice-cold NH_4Cl/brine solution and extracted twice with ethyl acetate. The combined organic extracts were dried over $MgSO_4$ and evaporated to dryness. Chromatotron chromatography on silica gel eluting with dichloromethane/hexane afforded *trans*-dibenzoylstilbene (**7**, 3.0 mg) and *cis*-dibenzoylstilbene (**6**, 12.2 mg) for a combined yield of 15.2 mg (57.3%). After recrystallization from ethanol, **6** had mp 216–217 °C (lit.[6] mp 215.9–216.3 °C) and **7** had mp 228–229.5 °C (lit.[7] mp 232–234 °C).

Reaction of the Ylide 5 with Meldrum's Acid. Preparation of 2-(4,4-Dimethyl-2,6-dioxo-3,5-dioxan-1-ylidene)-1,2-diphenylethanone (8). A solution of Meldrum's acid (24.47 mg, 0.163 mmol) and triethylamine (22.7 μL, 0.163 mmol) in 4 mL of THF was stirred for 30 min. A solution of **5** (60.0 mg, 0.163 mmol) in 4 mL of THF was immediately added dropwise to the enolate solution. The resulting mixture was stirred for 1 h at 0 °C and at room temperature for 3 days and then quenched as described above. Chromatotron chromatography on silica gel eluting with ethyl acetate/hexane afforded **8** (33.6 mg, 0.1 mmol, 61%) as colorless needles that were recrystallized from ethyl acetate/hexane: mp 197–198.5 °C; IR ($CHCl_3$) 3010, 1674, 1598, 1290 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.87 (s, 6 H), 7.26–7.59 (m, 8 H), 7.81 (d, J = 1.5 Hz, 1 H), 7.90 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.78 (q), 105.13 (s), 117.20 (s), 128.44 (d), 128.62 (d), 128.96 (d), 129.11 (d), 131.28 (s), 132.00 (s), 134.06 (d), 134.25 (d), 158.91 (s), 160.71 (s), 169.78 (s), 192.81 (s); UV (MeCN) λ_{max} 245 nm (ε = 18000); HRMS m/z calcd for $C_{20}H_{16}O_5$ (M^+) 336.0998, found 336.1018.

Oxidative Coupling of 2-(4-Phenylurazolyl)-1,2-diphenylethanone (9) with Meldrum's Acid. Preparation of 2-(4,4-Dimethyl-2,6-dioxo-3,5-dioxan-1-ylidene)-1,2-diphenylethanone (8). A solution of Meldrum's acid (24.4 mg, 0.169 mmol) and triethylamine (23.5 μL, 0.169 mmol) in 5 mL of DMF was cooled to 0 °C and stirred for 15 min. In a separate flask, the urazole **9**[2] (29.0 mg, 0.078 mmol) in 2 mL of DMF was treated with *tert*-butyl hypochlorite (9.3 μL, 0.078 mmol) at room temperature. To the resulting yellow-orange solution was added the enolate solution; the mixture was stirred at room temperature for 12 h, and quenched as described above. The residual DMF was removed at 40 °C under reduced pressure. Chromatotron chromatography on silica gel eluting with dichloromethane followed by recrystallization from dichloromethane/hexane afforded 13.1 mg (0.039 mmol, 50%) of **8** as colorless crystals, mp 197–198 °C.

Oxidative Coupling of 2-(4-Phenylurazolyl)-1,2-diphenylethanone (9) with Dimedone. Preparation of 2-(4,4-Dimethyl-2,6-dioxocyclohexan-1-ylidene)-1,2-diphenylethanone (10). A solution of dimedone (23.7 mg, 0.169 mmol) and triethylamine (23 μL, 0.166 mmol) in 5 mL of DMF was cooled to 0 °C and stirred for 15 min. The ylide was prepared from 29.0 mg of **9**[2] as described in the previous section, treated with the enolate solution, and the resulting mixture was stirred at room temperature for 5 h. Following quenching as described above, Chromatotron chromatography on silica gel of the residue afforded **10** (15.0 mg, 0.045 mmol, 58%) as yellow needles after recrystallization from dichloromethane/hexane: mp 153.6–155.0 °C; IR ($CHCl_3$) 3010, 2950, 1670 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.13 (s, 6 H), 2.58 (s, 2 H), 2.65 (s, 2 H), 7.32–7.34 (m, 3 H), 7.40–7.45 (m, 4 H), 7.52 (dd, J = 7.5 and 7.5 Hz, 1 H), 7.87 (d, J = 7.5 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.49 (q), 30.00 (s), 53.10 (t), 128.22 (d), 128.57 (d), 128.62 (d), 129.85 (d), 133.15 (d), 133.28 (s), 133.47 (d), 133.51 (s), 134.64 (s), 162.08 (s), 194.76 (s), 196.65 (s), 197.67 (s); UV (MeCN) λ_{max} 304 (shoulder, ε =

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5860), 284 (7420), 242 (16 500); HRMS m/z calcd for $C_{22}H_{20}O_3$ (M^+) 332.1412, found 332.1401.

Oxidative Coupling of 2-(4-Phenylurazolyl)-1,2-diphenylethanone (9) with Dimethyl Malonate. Preparation of 2-(1,3-Dimethoxy-1,3-dioxo-2-propylidene)-1,2-diphenylethanone (11). Dimethyl malonate (83.6 mg, 0.632 mmol) and sodium hydride (20.4 mg, 0.425 mmol) were mixed in 5 mL of DMF at 0 °C and stirred for 20 min. In a separate flask, urazole **9**[2] (50.7 mg, 0.137 mmol) in 2 mL of DMF was treated with *tert*-butyl hypochlorite (16.7 μL, 0.137 mmol) and cooled to −40 °C. The enolate solution was added via cannula, and the mixture was stirred at room temperature for 14 h and quenched as described above (evaporation of solvent at <40 °C). Chromatotron centrifugal chromatography of the residue on silica gel eluting with dichloromethane followed by recrystallization from dichloromethane/hexane afforded **11** (28.5 mg, 0.088 mmol, 64%) as colorless crystals: mp 120.0–120.7 °C; IR ($CHCl_3$) 3020, 2950, 1720, 1670 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.67 (s, 6 H), 7.34–7.53 (m, 8 H), 7.94–7.96 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.65 (q), 125.97 (s), 127.37 (d), 128.77 (d), 128.92 (d), 130.18 (d), 133.04 (s), 133.51 (d), 133.62 (d), 134.96 (s), 155.09 (s), 163.05 (s), 165.64 (s), 193.68 (s); UV (MeCN) λ_{max} 284 nm (ε = 11 050), 251 (20 320); HRMS m/z calcd for $C_{19}H_{16}O_5$ (M^+) 324.0998, found 324.1020.

Oxidative Coupling of 2-(4-Phenylurazolyl)-1,3-diphenyl-1,3-propanedione (12) with 1,3-Diphenyl-1,3-propanedione. Preparation of Tetrabenzoylethylene (13). Dibenzoylmethane (123.3 mg, 0.55 mmol) and sodium hydride (13.2 mg, 0.55 mmol) were dissolved in 5 mL of THF and stirred for 30 min. In a separate flask, urazole **12**[2] (100 mg, 0.25 mmol) was dissolved in 10 mL of THF and treated with *tert*-butyl hypochlorite (29.8 μL, 0.25 mmol). After about 1 min, the resulting yellow solution was transferred by cannula into the enolate solution, and the mixture was stirred for 2 days and then quenched as described above. Chromatography on 50 g of flash silica gel eluting with benzene afforded **13** (13 mg, 0.029 mmol, 11.7%), which after recrystallization from carbon disulfide had mp 185.5–186.5 °C (lit.[8] mp 182–183 °C) and was found to be identical with an authentic sample.

Oxidative Coupling of 2-(4-Phenylurazolyl)-1,3-diphenyl-1,3-propanedione (12) with Meldrum's Acid. Preparation of 2-(4,4-Dimethyl-2,6-dioxo-3,5-dioxan-1-ylidene)-1,3-diphenyl-1,3-propanedione (14). A solution of Meldrum's acid (172.9 mg, 1.2 mmol) and triethylamine (167.3 μL, 1.2 mmol) in 15 mL of THF at 0 °C was stirred for 30 min. The ylide was prepared from urazole **12**[2] (200.0 mg, 0.5 mmol) in 15 mL of THF, and mixed with the enolate solution as described in the above procedure. The reaction mixture was stirred for 1 h at 0 °C and then at room temperature for 7 h. Following quenching and extraction with dichloromethane as described above, chromatography on 30 g of flash silica gel at −10 °C eluting with dichloromethane afforded **14**. After recrystallization from dichloromethane/hexane, **14** (144.5 mg, 0.397 mmol, 79.4%) was obtained as colorless crystals: mp 200 °C dec; IR ($CHCl_3$) 3010, 1740, 1660, 1600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.82 (s, 6 H), 7.53 (dd, J = 7.5 and 7.5 Hz, 4 H), 7.65 (dd, J = 7.5 and 7.5 Hz, 2 H), 8.10 (d, J = 7 Hz, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.01 (q), 106.06 (s), 117.74 (s), 128.84 (d), 129.85 (d), 133.50 (s), 134.76 (d), 158.59 (s), 170.18 (s), 188.89 (s); UV (MeCN) λ_{max} 290 nm (ε = 6300), 252 (26 000); HRMS m/z calcd for $C_{21}H_{16}O_6$ (M^+) 364.0947, found 364.0943.

X-ray Structure Determination of 2-(4,4-Dimethyl-2,6-dioxo-3,5-dioxan-1-ylidene)-1,3-diphenyl-1,3-propanedione (14). A colorless crystal of **14** with dimensions of 0.20 × 0.20 × 0.50 mm was mounted in a glass capillary on a Nicolet R3m/V four-circle diffractometer (Mo Kα, λ = 0.710 73 Å, graphite monochromator). Unit cell parameters were determined from 15 well-centered reflections: (19° < 2θ < 26°), a = 9.371 (2) Å, b = 14.318 (5) Å, c = 13.721 (3) Å, β = 100.26 (2)°, V = 1811.5 (8) Å^3, and Z = 4. Axial photographs and a limited search through an octant of reciprocal space revealed systematic absences and symmetry consistent with the monoclinic space group $p2_1/c$ (No. 14). A quarter sphere of data (±h,+k,+l) was collected in the 2θ–θ scan mode with 2θ ranging from 3.0 to 45.0°. Scan speeds varied from 4.0 to 29.3 °/min. A total of 2629 reflections were measured and corrected for Lorentz and polarization effects, but not for absorption. The minimum and maximum drift corrections (based on a set of three standards measured for every 37 reflections) were 0.9819 and 1.0158, respectively. Data processing yielded 2387 unique reflections, of which 1713 had $F > 4\sigma(F)$ with R(int) = 0.0211 for the averaging of equivalent reflections.

The structure was successfully solved by a combination of direct methods (XS:TREF) and Fourier techniques in the monoclinic space group $p2_1/n$ (No. 14), and refined by full-matrix least squares. The nonhydrogen atoms were refined with anisotropic temperature parameters, hydrogen atoms were allowed to ride on their respective carbons [C–H = 0.96 Å, U(H) = 0.08], an extinction correction was made, and a weighting scheme based on $\sigma(F)$ was employed. The final residuals were $R(F)$ = 0.0409 and $R_w(F)$ = 0.0516 with a value of 1.19 for the goodness of fit. The largest and mean |shift/esd| in the final cycle were 0.001 and 0.000, and the minimum and maximum excursions in the final difference map were −0.14 and 0.13 e/Å^3.[9]

Oxidative Coupling of 2-(4-Phenylurazolyl)-1,3-diphenyl-1,3-propanedione (12) with Dimedone. Preparation of Bis(4,4-dimethyl-2-hydroxy-6-oxo-1-cyclohexen-1-yl)benzoylmethane (15). A solution of dimedone (98.7 mg, 0.705 mmol) and triethylamine (98 μL, 0.705 mmol) in 10 mL of THF at 0 °C was stirred for 25 min. In a separate flask, urazole **12**[2] (57.8 mg, 0.145 mmol) in 5 mL of THF was treated with *tert*-butyl hypochlorite (17.3 μL, 0.145 mmol) and cooled to 0 °C. This solution was added to the enolate solution, the mixture was stirred at room temperature for 12 h and then quenched and extracted with ethyl acetate as described above. Chromatotron chromatography on silica gel eluting with dichloromethane followed by recrystallization from dichloromethane/cyclohexane afforded **15** (27.0 mg, 0.068 mmol, 47%) as colorless crystals: mp 155.6–157.0 °C; IR ($CHCl_3$) 3200–2600, 1690, 1600 cm^{-1}. The NMR data for this compound suggest rapid equilibrium between the keto and enol forms. The O–H signals could not be observed in the proton NMR: ^1H NMR (300 MHz, $CDCl_3$) δ 0.97 (s, 12 H), 2.29 (s, 8 H), 5.47 (s, 1 H), 7.34 (dd, J = 7.2 and 7.2 Hz, 2 H), 7.44 (dd, J = 7.2 and 7.2 Hz, 1 H), 7.66 (dd, J = 7.0 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.08 (q), 31.38 (s), 39.60 (d), 46.26 (t), 113.63 (s), 127.80 (d), 128.18 (d), 132.00 (d), 137.31 (s), 190.10 (s), 196.80 (s); UV (MeCN) λ_{max} 256 nm (ε = 20 400); HRMS m/z calcd for $C_{24}H_{28}O_5$ (M^+) 396.1937, found 396.1960.

Oxidative Coupling of 3-(4-Phenylurazolyl)-2,4-pentanedione (16) with Meldrum's Acid. Preparation of *cis*-5-Acetyl-1-methyl-2,8-dioxa-3,7-dioxobicyclo[3.3.0]octane (17). A solution of Meldrum's acid (163.4 mg, 1.14 mmol) and triethylamine (158 μL, 1.14 mmol) in 5 mL of acetonitrile at 0 °C was stirred for 30 min. In a separate flask, urazole **16** (125 mg, 0.454 mmol) was dissolved in 8 mL of acetonitrile and treated with *tert*-butyl hypochlorite (54.2 μL, 0.454 mmol). After a few minutes, the enolate solution was added to the light pink ylide solution, and the mixture was stirred for 5 h and quenched as described above. Thick-layer chromatography on silica gel eluting with dichloromethane followed by recrystallization from dichloromethane/pentane afforded **17** (62 mg, 0.313 mmol) as colorless crystals: mp 192.0–192.5 °C; IR ($CHCl_3$) 1812, 1718, 1289 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.62 (s, 3 H), 2.30 (s, 3 H), 2.86 (d, J = 18.6 Hz, 2 H), 3.37 (d, J = 18.6 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.95 (q), 27.65 (q), 37.61 (t), 59.98 (s), 112.40 (s), 171.99 (s), 204.49 (s); HRMS m/z calcd for $C_9H_{10}O_5$ (M^+) 198.0528, found 198.0518.

X-ray Structure Determination of *cis*-5-Acetyl-1-methyl-2,8-dioxa-3,7-dioxobicyclo[3.3.0]octane (17). A colorless crystal of **17** was cut to roughly 0.05 × 0.25 × 0.25 mm in size, mounted on a glass fiber with epoxy cement, and transferred to a Siemens R3m/V four-circle diffractometer (Mo Kα, λ = 0.710 73 Å, graphite monochromator). Unit cell parameters were determined from the angular settings of 25 well-centered reflections (21° < 2θ < 28°): a = 10.5151 (10), b = 7.8361 (9), c = 11.6741 (13) Å, β = 110.687 (8)°, and V = 899.9 (2) Å^3. Axial photographs and a limited search through an octant of reciprocal space revealed systematic absences and symmetry consistent with the monoclinic space group $p2_1/c$ (No. 14). One quadrant of data (±h,+k,+l) was collected in the 2θ–θ scan mode with 2θ ranging from 3.0 to 55.0°. Scan speeds were varied from 1.5 to 4.0°/min. A total of 2340 reflections were measured and corrected for Lorentz and polarization effects, but not for absorption. The minimum and maximum drift corrections (based on a set of three standards measured for every 37 reflections) were 1.0000 and 1.0208, respectively. Data processing yielded 2082 unique reflections, of which 1546 had $F > 3\sigma(F)$ with R(int) = 0.0090 for the averaging of equivalent reflections. The structure was successfully solved by direct methods (XS:TREF) in the monoclinic space group $P2_1/c$ (No. 14), and refined by full-matrix least squares. The non-hydrogen atoms were refined with anisotropic temperature parameters, the hydrogen atom coordinates and individual isotropic temperature parameters were free to vary, an extinction correction was made, and a weighting scheme based on $\sigma(F)$ was employed. The final residuals were $R(F)$ = 0.0497 and $R_w(F)$ = 0.0401 with a value of 1.59 for the goodness of fit. The largest and mean |shift/esd| in the final cycle were 0.001 and 0.000, and the minimum and maximum excursions in the final difference map were −0.20 and 0.27 e/Å^3, respectively.

Oxidative Coupling of 2-(4-Phenylurazolyl)-5,5-dimethyl-1,3-cyclohexanedione (18) with Dimedone. Preparation of the Tris(dimedone) Coupling Product 19. A solution of dimedone (33.3 mg, 0.24 mmol) and triethylamine (33.1 μL, 0.24 mmol) in 3 mL of acetonitrile at 0 °C was stirred for 30 min. In a separate flask, urazole **18** (30.0 mg, 0.1 mmol) was dissolved in 5 mL of acetonitrile and treated with *tert*-butyl hypochlorite (11.4 μL, 0.1 mmol). After 5 min, the aforementioned enolate solution was added to the pink ylide solution, and the mixture was stirred

for 18 h and quenched as described above. Thick-layer silica gel chromatography eluting with 50% ethyl acetate/hexane followed by recrystallization from dichloromethane/hexane afforded **19** (23.0 mg, 0.055 mmol, 55%) as colorless crystals: mp 201–203 °C; IR ($CHCl_3$) 2962, 1617, 1398 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.05 (s, 6 H), 1.11 (s, 6 H), 1.12 (s, 6 H), 1.78 (d, J = 15 Hz, 2 H), 1.88 (d, J = 15 Hz, 2 H), 2.21 (d, J = 15 Hz, 2 H), 2.35 (d, J = 15 Hz, 2 H), 2.33 (d, J = 18 Hz, 2 H), 2.49 (d, J = 18 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.8 (q), 29.0 (q), 31.4 (s), 34.8 (s), 38.7 (t), 43.8 (t), 51.2 (t), 62.0 (s), 112.0 (s), 116.9 (s), 177.7 (s), 198.7 (s); HRMS m/z calcd for $C_{24}H_{32}O_6$ (M^+) 416.2199, found 416.2219.

Deurazolation of the Bis(urazole) Adduct of Meldrum's Acid (30) [2,2-Bis(4-phenylurazolyl)-5,5-dimethyl-4,6-dioxa-1,3-cyclohexanedione]. Preparation of the Triethylamine Salt of 2-(4-Phenylurazolyl)-5,5-dimethyl-4,6-dioxa-1,3-cyclohexanedione (20). To a solution of the bis(urazole) adduct of Meldrum's acid (**30**)[2] (60.0 mg, 0.12 mmol) in 2 mL of THF at 0 °C was added triethylamine (84.0 μL, 0.6 mmol). Upon warming to room temperature, **20** precipitated from the reaction mixture. Collection by filtration afforded **20** (47 mg, 0.11 mmol, 92%) as a colorless powder, which was recrystallized from dichloromethane/ethyl acetate: mp 150 °C dec; IR ($CHCl_3$) 3012 (vb), 1703, 1625, 1502 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$/DMSO) δ 1.21 (t, J = 7.5 Hz, 9 H), 1.75 (s, 6 H), 3.07 (q, J = 7.5 Hz, 6 H), 7.30–7.65 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$/DMSO) δ 8.2 (q), 25.5 (q), 45.6 (t), 102.1 (s), 107.0 (s), 125.2 (d), 125.5 (d), 127.1 (s), 128.4 (d), 151.3 (s), 151.6 (s), 164.7 (s). The structure of **20** has been confirmed by the single-crystal X-ray analysis described below.

X-ray Structure Determination of the Triethylamine Salt of 2-(4-Phenylurazolyl)-5,5-dimethyl-4,6-dioxa-1,3-cyclohexanedione (20). A colorless plate of the salt **20** was cut to 0.05 × 0.22 × 0.48 mm and mounted on a glass fiber on a Siemens R3m/V four-circle diffractometer (Mo Kα, λ = 0.71073 Å, graphite monochromator). Unit cell parameters were determined from the angular settings of 25 well-centered reflections (20° < 2θ < 26°); a = 18.224 (2), b = 10.555 (2), c = 22.913 (3) Å, β = 94.214 (9)°, and V = 4395.4 (9) Å^3. Axial photographs and a limited search through an octant of reciprocal space revealed systematic absences and symmetry consistent with the monoclinic space group $p2_1/n$. One quadrant of data ($\pm h$,+k,+l) was collected in the 2θ–θ scan mode with 2θ ranging from 3.0 to 45.0°. Scan speeds varied from 2.0 up to 8.0°/min. A total of 6334 reflections were measured and corrected for Lorentz and polarization effects, but not for absorption. The minimum and maximum drift corrections (based on a set of three standards measured for every 37 reflections) were 0.9701 and 1.0027, respectively. Data processing yielded 5778 unique reflections, of which 3842 had $F > 3\sigma(F)$ with R(int) = 0.0155 for the averaging of equivalent reflections.

The structure was successfully solved by direct methods (XS:TREF) in the monoclinic space group $p2_1/n$ (No. 14) and refined by full-matrix least squares. The non-hydrogen atoms were refined with anisotropic temperature parameters, hydrogen atoms were allowed to ride on their respective carbons (C–H = 0.96 Å), and a weighting scheme based on $\sigma(F)$ was employed. All hydrogen atoms were assigned fixed isotropic temperature parameters U(H) = 0.08. The coordinates of the N-bound hydrogens were free to vary. The final residuals were $R(F)$ = 0.0755 and $R_w(F)$ = 0.0765 with a value of 1.42 for the goodness of fit. The largest and mean |shift/esd| in the final cycle were 0.001 and 0.000, and the minimum and maximum excursions in the final difference map were −0.37 and 0.45 e/Å^3, respectively.

The atoms for one of the two triethylammonium cations exhibited large thermal motions. Attempts to locate a suitable disorder model were unsuccessful. The atoms were eventually reset and refined as fully occupied sites with anisotropic temperature parameters. The resulting short C–C distances are attributed to the large anisotropies observed.

Oxidative Coupling of the Triethylamine Salt of 2-(4-Phenylurazolyl)-5,5-dimethyl-4,6-dioxa-1,3-cyclohexanedione (20) with Meldrum's Acid. Preparation of the Bis(Meldrum's acid) Coupling Product 21 [2-(4,4-Dimethyl-2,6-dioxo-3,5-dioxan-1-yldene)-5,5-dimethyl-4,6-dioxa-1,3-cyclohexadione]. A solution of Meldrum's acid (97.0 mg, 0.675 mmol) and triethylamine (94.0 μL, 0.675 mmol) in 5 mL of DMF was cooled to 0 °C and stirred for 30 min. In a separate flask, the salt **20** (113.0 mg, 0.27 mmol) in 5 mL of DMF was treated with *tert*-butyl hypochlorite (32.2 μL, 0.27 mmol) at 0 °C. The resulting light pink ylide soluton was added to the enolate solution and the mixture was allowed to stir for 12 h, during which time a colorless precipitate formed. The precipitate was collected by filtration and washed several times with ether to give **21** (6.0 mg, 0.02 mmol, 7%) as a colorless powder: mp 210 °C dec (lit.[15] mp 200 °C and decomposition with gas evolution at 215–225 °C); superimposable infrared and mass spectra and undepressed mixture mp with authentic sample of **21**.

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Oxidative Coupling of the Triethylamine Salt of 2-(4-Phenylurazolyl)-5,5-dimethyl-4,6-dioxa-1,3-cyclohexanedione (20) with 1,3-Diphenyl-1,3-propanedione. Preparation of 2-(4,4-Dimethyl-2,6-dioxo-3,5-dioxan-1-ylidene)-1,3-diphenyl-1,3-propanedione (14). A solution of dibenzoylmethane (26.7 mg, 0.119 mmol) and sodium hydride (3.0 mg, 0.125 mmol) in 3 mL of acetonitrile was cooled to 0 °C and stirred for 30 min. In a separate flask, the salt **20** (20 mg, 0.047 mmol) in 3 mL of acetonitrile was treated with *tert*-butyl hypochlorite (5.6 μL, 0.047 mmol) at 0 °C. The resulting light pink ylide solution was added to the enolate solution, the mixture was allowed to come slowly to room temperature and stirred for 18 h then quenched as described above. Thick-layer chromatography eluting with 50% dichloromethane/hexane at 0 °C gave **14** (7.0 mg, 0.019 mmol, 40%) as colorless crystals having mp 200 °C dec.

Oxidative Coupling of 2-(4-Phenylurazolyl)cyclohexanone (22) with Meldrum's Acid. Preparation of 2-(4,4-Dimethyl-2,6-dioxo-3,5-dioxan-1-yl)-2-cyclohexen-1-one (23). A solution of Meldrum's acid (30.6 mg, 0.212 mmol) and triethylamine (26.6 μL, 0.191 mmol) in 6 mL of acetonitrile was stirred at room temperature for 20 min. In a separate flask, the urazole **22**[2] (26.0 mg, 0.095 mmol) in 12 mL of acetonitrile was treated with *tert*-butyl hypochlorite (11.4 μL, 0.095 mmol). After several minutes, the enolate solution was added to the resulting pale orange ylide solution. The mixture was stirred for 12 h and poured into brine, several drops of dilute HCl were added, and the solution was extracted with ethyl acetate. Chromatotron chromatography on silica gel eluting first with dichloromethane and then with 25% ethyl acetate/dichloromethane afforded 2.6 mg of the starting urazole **22** and 11.8 mg (0.050 mmol, 58% based on recovered starting urazole) of **23** as colorless crystals: mp 151.0–152.3 °C; IR ($CHCl_3$) 2940, 1750, 1680 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.81 (s, 3 H), 1.86 (s, 3 H), 2.12 (dt, J = 13.2 and 6.3 Hz, 2 H), 2.49–2.56 (m, 4 H), 4.07 (s, 1 H), 7.09 (t, J = 4 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.53 (t), 26.09 (t), 27.45 (q), 28.08 (q), 37.11 (t), 48.74 (d), 105.43 (s), 133.19 (s), 152.41 (d), 164.44 (s), 196.47 (s): HRMS m/z calcd for $C_{12}H_{14}O_5$ (M^+) 238.0841, found 238.0834.

Oxidative Coupling of 2-(4-Phenylurazolyl)cyclohexanone (22) with Dimedone. Preparation of the Bis(dimedone) Coupling Product of Cyclohexanone 24. A solution of dimedone (77.0 mg, 0.55 mmol) and triethylamine (62 μL, 0.44 mmol) in 10 mL of DMF was stirred at 0 °C for 20 min. In a separate flask, the urazole **22**[2] (60.7 mg, 0.22 mmol) in 8 mL of DMF was treated with *tert*-butyl hypochlorite (26.5 μL, 0.22 mmol). After 3 min, this solution was cooled to 0 °C, the enolate solution added, and the resulting solution stirred for 14 h. Upon evaporation to dryness at 45 °C under reduced pressure, the residue was purified by Chromatotron chromatography on silica gel, eluting with dichloromethane/ethyl acetate (5:1) to afford the bis adduct **24** (56.2 mg, 0.16 mmol, 71%) as colorless crystals after recrystallization from dichloromethane/cyclohexane: mp 132.9–133.7 °C; IR ($CHCl_3$) 2950, 1670, 1650, 1390 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.06 (s, 6 H), 1.08 (s, 6 H), 1.40 (dt, J = 13.5 and 6.8 Hz, 2 H), 1.51 (dt, J = 13.5 and 6.8 Hz, 2 H), 2.01 (t, J = 6.6 Hz, 2 H), 2.15–2.41 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.31 (t), 16.75 (t), 25.70 (t), 28.05 (q), 28.07 (t), 28.67 (q), 33.73, (s), 37.52 (t), 51.70 (t), 55.32 (s), 116.86 (s), 124.17 (s), 173.28 (s), 192.37 (s); UV (MeCN) λ_{max} 245 nm (ϵ = 20600); HRMS m/z calcd for $C_{22}H_{28}O_4$ (M^+) 356.1988, found 356.1988.

Oxidative Coupling of 3-(4-Phenylurazolyl)-2-oxoindoline (25) with Dimedone. Preparation of the Bis(dimedone) Coupling Product of Oxindole 26. A solution of dimedone (29.2 mg, 0.21 mmol) and triethylamine (29 μL, 0.21 mmol) in 5 mL of DMF was stirred at 0 °C for 15 min. In a separate flask, the urazole **25**[2] (25.9 mg, 0.084 mmol) in 10 mL of DMF was cooled to 0 °C and treated with *tert*-butyl hypochlorite (10 μL, 0.085 mmol). The resulting red solution was stirred for 1 min, the enolate solution was added, the resulting mixture was stirred at room temperature for 12 h, and quenched as described above. Chromatotron chromatography on silica gel eluting with dichloromethane/ethyl acetate (5:1) followed by recrystallization from dichloromethane/cyclohexane afforded 31.6 mg (0.077 mmol, 92%) of **26** as colorless crystals: mp 237 °C dec; IR ($CHCl_3$) 3410, 3400–2850, 1725, 1680, 1650, 1600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.03 (s, 3 H), 1.07 (s, 3 H), 1.13 (s, 6 H), 2.05–2.49 (m, 8 H), 3.53 (s, 1 H), 6.80–6.94 (m, 3 H), 7.13–7.19 (m, 1 H), 8.54 (s, 1 H), 8.92 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.71 (q), 26.92 (q), 29.26 (q), 31.41 (s), 33.04 (q), 33.64 (s), 43.22 (t), 46.59 (s), 48.00 (t), 50.64 (t), 54.79 (t), 60.44 (d), 100.82 (s), 110.39 (d), 111.87 (s), 120.46 (d), 122.35 (d), 128.34 (d), 132.36 (s), 143.24 (s), 168.93 (s), 181.39 (s), 195.24 (s), 202.36 (s); UV (MeCN) λ_{max} 253 nm (ϵ = 18900), 213 (20300); HRMS m/z calcd for $C_{24}H_{27}NO_5$ (M^+) 409.1889, found 409.1887.

X-ray Structure Determination of the Bis(dimedone) Adduct 26. A crystal of **26** with approximate dimensions of 0.12 × 0.22 × 0.28 mm was lightly coated with epoxy (crystals of **26** were found to decompose over time, possibly due to temperature sensitivity and/or solvent loss) prior

to being mounted on a glass fiber, which in turn was transferred to a Nicolet R3m/V four-circle diffractometer (Mo Kα, λ = 0.71073 Å), graphite monochromator). Unit cell parameters were determined from 15 well-centered reflections (15° < 2θ < 22°); $a = b = 21.847$ (4) Å, $C = 22.530$ (6) Å, $V = 10780$ (5) Å^3, and $Z = 16$. Axial photographs and a limited search through an octant of reciprocal space revealed systematic absences and symmetry consistent with the tetragonal space group $I4_1/a$ (No. 88). One octane of data ($+h,+k,+l$) was collected in the 2θ–θ scan mode with 2θ ranging from 3.0 to 45.0°. Scan speeds varied from 2.0 to 29.3 °/min. A total of 7771 reflections were measured and corrected for Lorentz and polarization effects, but not for absorption. The minimum and maximum drift corrections (based on a set of three standards measured for every 37 reflections) were 0.9073 and 1.0065, respectively. Data processing yielded 3549 unique reflections, of which 1717 had $F > 4\sigma(F)$ with R(int) = 0.0275 for the averaging of equivalent reflections.

The structure was successfully solved by a combination of direct methods (XS:TREF) and Fourier techniques in the tetragonal space group $I4_1/a$ (No. 88), and refined by full-matrix least-squares. The non-hydrogen atoms were refined with anisotropic temperature parameters, hydrogen atoms were allowed to ride on their respective carbons [C–H = 0.96 Å, U(H) = 0.08], and a weighting scheme based on $\sigma(F)$ was employed. The coordinates of the amine and hydroxy H atoms H(1) and H(30) were free to vary. The final residuals were $R(F) = 0.0809$ and $R_w(F) = 0.0781$ with a value of 1.50 for the goodness of fit. The largest and mean |shift/esd| in the final cycle were 0.001 and 0.000, and the minimum and maximum excursions in the final difference map were −0.43 and 0.53 e/Å^3, respectively.[9]

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Registry No. 5, 135257-61-3; (*Z*)-**6**, 6313-26-4; (*E*)-**7**, 10496-80-7; **8**, 135257-62-4; **9**, 123209-01-8; **10**, 91301-41-6; **11**, 131266-01-8; **12**, 72708-78-2; **13**, 5860-38-8; **14**, 135257-63-5; **15**, 123271-58-9; **16**, 72708-71-5; *cis*-**17**, 135257-64-6; **18**, 135257-65-7; **19**, 135257-66-8; **20**, 135257-68-0; **21**, 23340-29-6; **22**, 98186-09-5; **23**, 135257-69-1; **24**, 135257-70-4; **25**, 123209-00-7; (±)-**26**, 135257-71-5; PTAD, 15988-11-1; PhCO, 3469-17-8; $PhCOCH_2Ph$, 451-40-1; $MeOCOCH_2COOMe$, 108-59-8; $PhCOCH_2COPh$, 120-46-7; Meldruma's acid, 2033-24-1; dimedone, 126-81-8.

Supplementary Material Available: X-ray data for **14**, **17**, **20**, and **26**, figures listing the atomic numbering scheme, and tables for each compound, including (1) X-ray structure determination summary, (2) atomic positional parameters, (3) bond distances, (4) bond angles, (5) anisotropic temperature factors, and (6) hydrogen positional parameters (46 pages). Ordering information is given on any current masthead page.

Rate–Equilibrium Correlations for the Aldol Condensation: An Analysis in Terms of Marcus Theory

J. Peter Guthrie

Contribution from the Department of Chemistry, University of Western Ontario, London, Ontario, Canada N6A 5B7. *Received November 13, 1990. Revised Manuscript Received May 28, 1991*

Abstract: Both the addition and elimination steps of the intermolecular aldol condensation show approximate agreement with Marcus theory. The calculations are performed for reaction of an encounter complex of enolate and a carbonyl acceptor to give the alkoxide anion of the adduct for the addition reaction and of the enolate anion of the adduct to give the encounter complex of enone and hydroxide ion for the elimination reaction. The intrinsic barriers for these reactions are 13.89 ± 0.80 kcal/mol for the addition reaction and 14.13 ± 0.49 kcal/mol for the elimination reaction. Estimated equilibrium constants are used to predict rate constants for some simple aldol reactions. Large effects of polar substituents on the rates of aldol condensations can be predicted.

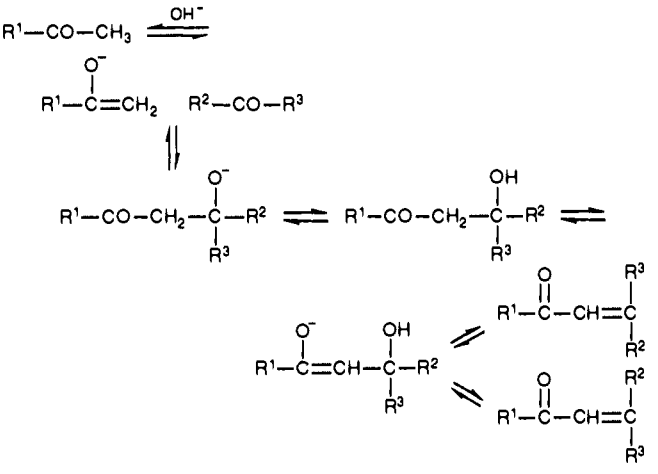
Introduction

The aldol condensation is an extremely important synthetic reaction, as witnessed by the entire volume of *Organic Reactions* required to review it.[1] There has been no method for making even semiquantitative predictions for the rates of the individual steps. Some years ago, we reported[2] equilibrium constants for a set of simple aldol condensations, eq 1, and demonstrated several methods for estimating equilibrium constants for these reactions.

$$R^1COCH_3 + R^2COR^3 \overset{HO^-}{\rightleftharpoons} R^1COCH_2{-}C(OH)R^2R^3 \overset{HO^-}{\rightleftharpoons} R^1COCH{=}C(R^2)(R^3) \quad (1)$$

We[3-9] and others[10-32] have carried out detailed analyses of the kinetics of a series of simple aldol condensations, which now provide a solid basis for developing methods for predicting rates.

Scheme I



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