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The Michael Reaction of Acetophenones with *trans*-Dibenzoylethylene

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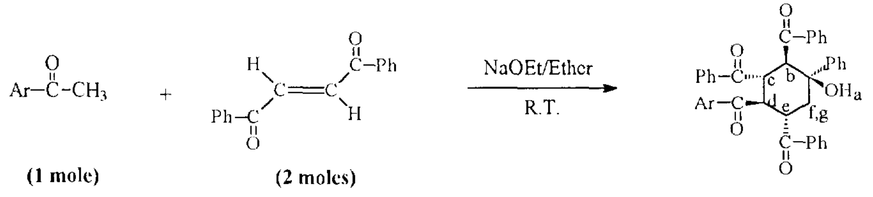
Abstract: The synthesis of a series of highly substituted cyclohexane derivatives has been carried out in a single one-pot reaction of acetophenones and *trans*-dibenzoylethylene (1:2) using sodium ethoxide in anhydrous diethyl ether at room temperature to give 4-aroyl-2,3,5-tribenzoyl-1-phenylcyclohexanols. A structural assignments was achieved from the elemental analysis, infrared, and proton nuclear magnetic resonance spectroscopy. The single crystal x-ray crystallography clearly shows the highly substituted cyclohexane ring.

The Michael reaction is perhaps one of the most general method used for C-C bond formation[1]. An extensive literature survey indicates that there has been a large amount of work reported on the condensation of α,β-unsaturated Michael acceptors with active methylene compounds[2-6]. For example, α,β-unsaturated aromatic ketones react with malononitrile[7], ethyl cyanoacetate[8], thioacetamide[9], cyanoacetamide[10], to give cyanopyridines, 2-pyridine thiones and 2-pyridones. Furthermore, the preparative value of one-pot, multicomponent, sequential Michael-Michael ring closure reactions followed by aromatization is illustrated by a total synthesis of juncunol, an unusual vinyldihydrophenanthrene [11]. As a result of our continued interest in these condensations, we recently reported the synthesis of substituted pyridines, 2-pyridones, and highly substituted cyclohexanes derivatives via the condensation of different chalcones with a variety of active methylene compounds[12-17]. In addition, several novel bicyclo[2.2.2]lactones[18], were synthesized from a facile one-pot reaction by the condensation of *trans*-dibenzoylethylene and different arylacetonitriles in basic medium. The reaction proved to be convenient and gives high yield. To expand this work, we now report that the condensation of different acetophenones **1** with *trans*-dibenzoylethylene **2** using sodium ethoxide in dry diethyl ether at room temperature yields 4-aroyl-2,3,5-tribenzoyl-1-phenylcyclohexanols **3**, as shown in scheme 1. This facile reaction was carried out at room temperature in 1:2 molar ratio of the acetophenones and trans-dibenzoylethylene , respectively. Upon stirring of the reactants for 15-30 minutes, heavy precipitates were formed which upon workup and crystallization from glacial acetic acid or aqueous acetic acid afforded good yields of the substituted cyclohexanols products. The stoichiometry of the reaction was revealed by the ^{1}H-NMR spectra of the product and by the single crystal x-ray crystallography as well. Although we have not undertaken a mechanistic investigation of the reaction, it is proposed that the cyclohexanols arise from a double Michael-addition of acetophenones **1** to two molecules of *trans*-dibenzoylethylene **2** to give a bis-adduct which then undergoes an intramolecular aldol cyclization to give the cyclohexanols **3**, as shown in scheme 2.

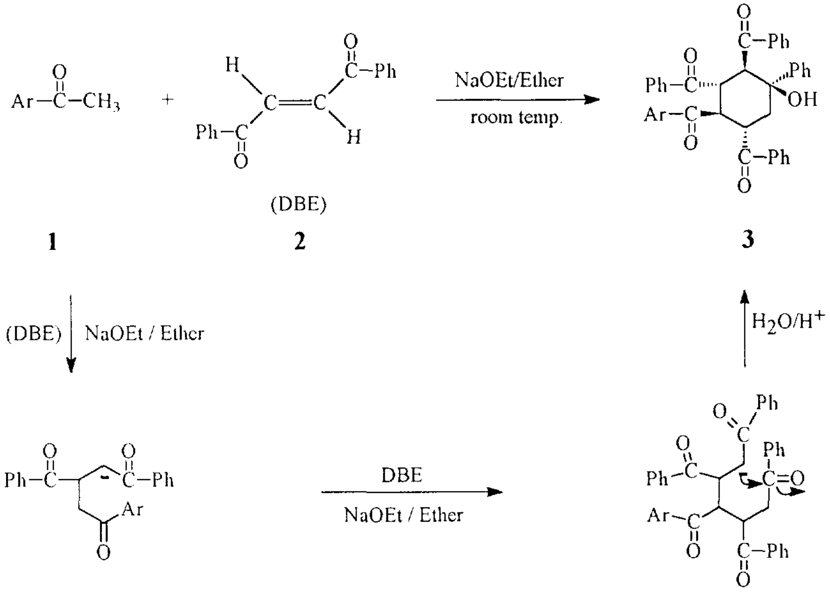


1 **2** **3**

3	**Ar**
a	2-Bromophenyl
b	4-Bromophenyl
c	4-Flourophenyl
d	4-Chlorophenyl
e	2,4-Dichlorophenyl
f	2,5-Dichlorophenyl
g	3,4-Dichlorophenyl
h	3,4-Dimethoxyphenyl

Scheme **1**

The structures of these cyclohexanol derivatives have been established on the basis of their elemental analysis, infrared and proton nuclear magnetic resonance spectral data as well as single crystal x-ray crystallography. The infrared spectra of the products **3** showed a peak at $\nu = 3550\text{-}3600$ cm^{-1} due to the stretching hydroxyl group, another broad peak at $\nu = 1650\text{-}1690$ cm^{-1} characteristic of the stretching frequency of the aroyl carbonyl group was also observed. The proton nuclear magnetic resonance spectra were also in agreement with the suggested structures. As a representative example, the ^{1}H NMR spectrum of **3**e showed a doublet of doublet at $\delta = 2.15\text{-}2.29$ due to H_f and H_g, ($J_{fg} = 13.0$ *Hz)*. Another multiplet at $\delta = 4.42\text{-}5.28$ integrating for five protons H_b, H_c, H_d, H_e and the hydroxylic proton H_a was also appeared. The aromatic protons observed as a multiplet at $\delta = 6.97\text{-}8.02$. The x-ray molecular plot of the same molecule is given in the figure which clearly shows the cyclic structure of the cyclohexanol derivative **3**e. Tables 1, 2 and 3 show the bond angles, bond lengths and H-atom coordinates (x 10^4) and isotropic displacement coefficients (Å^2 x 10^3) for the same molecule. The presence of the hydroxyl proton overlapping with the other four protons of the cyclohexane ring was confirmed by adding few drops of deuterium oxide to the NMR sample tube then running the NMR scanning again, as a result the integration of the multiplet was decreased by one proton. The central cyclohexane ring of **3** has a chair conformation with all substituents in equatorial position except the OH group and it is believed that the all-equatorial products are formed under kinetic control.



Scheme 2

Table 1. Bond angles (°)

C(2)-C(1)-C(6)	117.7(9)	C(2)-C(1)-C(7)	121.3(10)
C(6)-C(1)-C(7)	120.9(10)	C(1)-C(2)-C(3)	121.4(12)
C(2)-C(3)-C(4)	119.6(13)	C(1)-C(4)-C(3)	119.8(12)
C1(1)-C(4)-C(5)	118.0(11)	C(3)-C(4)-C(5)	122.1(11)
C(4)-C(5)-C(6)	118.1(13)	C1(2)-C(6)-C(1)	122.9(8)
C1(2)-C(6)-C(5)	115.9(11)	C(1)-C(6)-C(5)	121.0(12)
O(1)-C(7)-C(1)	121.9(10)	O(1)-C(7)-C(8)	120.8(7)
C(1)-C(7)-C(8)	117.3(9)	C(7)-C(8)-C(9)	109.5(8)
C(7)-C(8)-C(13)	109.6(8)	C(9)-C(8)-C(13)	110.8(7)
C(8)-C(9)-C(10)	109.9(8)	C(8)-C(9)-C(14)	109.6(7)
C(10)-C(9)-C(14)	109.9(8)	C(9)-C(10)-C(11)	111.8(7)
C(9)-C(10)-C(21)	108.8(8)	C(11)-C(10)-C(21)	110.9(7)
O(4)-C(11)-C(10)	109.9(8)	O(4)-C(11)-C(12)	104.3(8)
C(10)-C(11)-C(12)	108.8(7)	O(4)-C(11)-C(28)	113.5(6)
C(10)-C(11)-C(28)	111.1(8)	C(12)-C(11)-C(28)	108.9(8)
C(11)-C(12)-C(13)	113.1(8)	C(8)-C(13)-C(12)	110.2(7)
C(8)-C(13)-C(34)	110.5(7)	C(12)C(13)-C(34)	107.3(8)
O(2)-C(14)-C(9)	118.9(9)	O(2)-C(14)-C(15)	119.6(6)
C(9)-C(14)-C(15)	121.5(8)	C(14)-C(15)-C(16)	117.5(3)
C(14)-C(15)-C(20)	122.5(3)	O(3)-C(21)-C(10)	119.2(8)
O(3)-C(21)-C(22)	119.0(9)	C(10)-C(21)-C(22)	121.8(8)
C(21)-C(22)-C(23)	122.1(5)	C(21)-C(22)-C(27)	117.7(5)
C(11)-C(28)-C(29)	119.6(4)	C(11)-C(28)-C(33)	120.3(4)
O(5)-C(34)-C(13)	121.0(7)	O(5)-C(34)-C(35)	121.1(9)
C(13)-C(34)-C(35)	117.9(7)	C(34)-C(35)-C(36)	122.5(5)
C(34)-C(35)-C(40)	117.4(5)		

Table 2 . Bond lengths (Å)

Cl(1)-C(4)	1.765 (12)	Cl(2)-C(6)	1.720 (13)
O(1)-C(7)	1.200 (13)	O(2)-C(14)	1.211 (11)
O(3)-C(21)	1.227 (12)	O(4)-C(11)	1.431 (11)
O(5)-C(34)	1.219 (10)	C(1)-C(2)	1.354 (17)
C(1)-C(6)	1.400 (17)	C(1)-C(7)	1.520 (12)
C(2)-C(3)	1.371 (14)	C(3)-C(4)	1.340 (23)
C(4)-C(5)	1.359 (23)	C(5)-C(6)	1.377 (15)
C(7)-C(8)	1.524 (16)	C(8)-C(9)	1.537 (14)
C(8)-C(13)	1.542 (9)	C(9)-C(10)	1.556 (15)
C(9)-C(14)	1.514 (10)	C(10)-C(11)	1.551 (10)
C(10)-C(21)	1.514 (15)	C(11)-C(12)	1.532 (14)
C(11)-C(28)	1.496 (15)	C(12)-C(13)	1.530 (15)
C(13)-C(34)	1.536 (14)	C((14)-C(15)	1.496 (13)
C(21)-C(22)	1.498 (11)	C(34)-C(35)	1.476 (9)

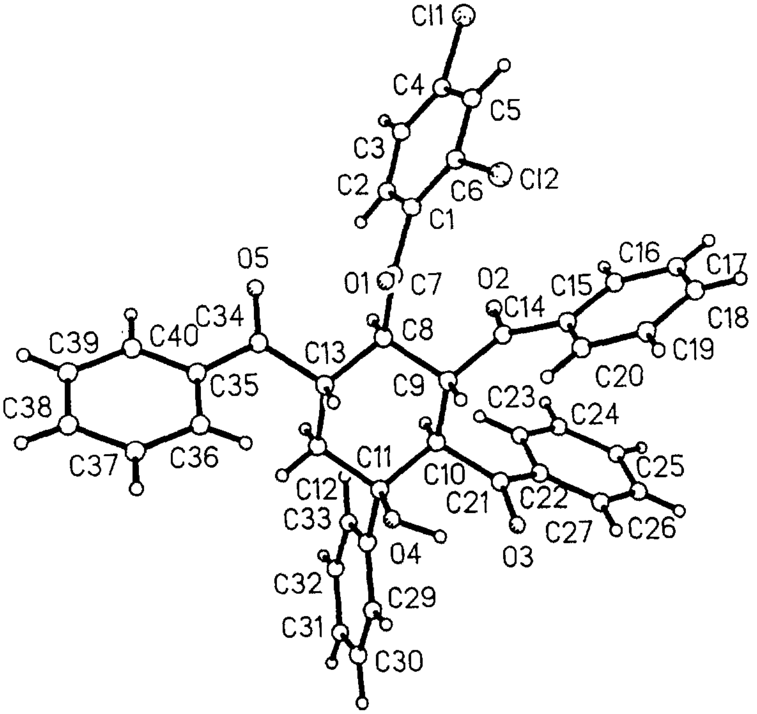


Figure. Single crystal x-ray plot of **3e** ($C_{40}H_{30}Cl_2O_5$).

Table 3. H-Atom coordinates (x10^4) and isotropic displacement coefficients (Å^2 x 10^3).

	X	y	z	U
H(4)	4946	4122	10768	50
H(2A)	-673	3933	7848	40
H(3A)	-2589	3015	6297	40
H(5A)	-646	3042	4283	40
H(8A)	964	4067	8943	40
H(9A)	3334	3771	8871	40
H(10A)	1833	2751	9862	40
H(12A)	1838	4927	11067	40
H(12B)	3129	5950	11686	40
H(13A)	3299	5940	10035	40
H(16A)	818	288	5984	40
H(17A)	1616	- 503	4557	40
H(18A)	3627	550	4684	40
H(19A)	4841	2394	6237	40
H(20A)	4043	3185	7664	40
H(23A)	946	965	9423	40
H(24A)	-75	-1166	8715	40
H(25A)	1068	-2601	8278	40
H(26A)	3232	-1905	8549	40
H(27A)	4254	226	9257	40
H(29A)	5351	4418	12589	40
H(30A)	5467	4006	14160	40
H(31A)	3596	3267	14449	40
H(32A)	1610	2939	13167	40
H(33A)	1494	3350	11597	40
H(36A)	4195	7787	11161	40
H(37A)	5123	9864	12431	40
H(38A)	3836	11079	13030	40
H(39A)	1622	10217	12360	40
H(40A)	694	8140	11091	40

EXPERIMENTAL

All reagents were of commercial quality from freshly opened containers. Acetophenones and dibenzoylethylene were purchased from Aldrich Chemical Co. Reagent quality solvents were used without further purification. IR spectra were recorded as KBr disk using a Pye-Unicam SP3-100 instrument. ^{1}H-NMR spectra were run on a Bruker WP 80-SY instrument. Compounds were analyzed at M-H-W Laboratories, Phoenix, Arizona , USA. Melting points were determined on an ELECTROTHERMAL melting point apparatus and are uncorrected. All coupling constants (*J*) are in Hz.

1S*,2R*,3R*,4R*,5R*-(±)-4-Aroyl-2,3,5-tribenzoyl-1-phenylcyclohexanol 3a-h.

General Procedure:

To a suspension of NaOEt (680 mg, 0.01 mol) in anhydrous Et_2O (200 mL) containing acetophenones **1** (0.01 mol) was added the *trans*-dibenzoylethylene **2** (4.72 g, 0.02 mol). The mixture was stirred at r.t. for 15-30 min., the solid formed was filtered off and crystallized form glacial acetic acid The filtrate was poured into water (100 mL), the organic layer separated, dried (Na_2SO_4) and evaporated to give the crude unreacted starting materials.

X-ray analysis of (3e)[19]: The summary of crystal data, data collection, solution and refinement for this compound are as follows: empirical formula, $C_{40}H_{30}O_5Cl_2$ 0.15 H_2O; color and habit, colorless blocks; crystal size (mm), 0.13 x 0.20 x 0.38; crystal system, triclinic; space group, P1; unit cell dimensions; a(Å), 11.434 (2); b(Å), 12.050 (2); c(Å), 13.765(3); α(deg), 110.09(2) β(deg), 105.09(2); γ (deg), 100.08 (2); volume (A^3), 1644.8 (5); Z,2; density (calc.), 1.336 Mg /m^3; absorption coefficient, 2.142 mm^{-1}; F(000), 688; T, 198K; reflections collected, 4418; independent reflections, 4411; observed reflection , 2165 ($F> 4.0\ \sigma (F)$); absorption correction, XABS[20]. The system used: Siemens SHELXTL PLUS [21,22] (VMS); Refinement method, Full-matrix-least-squares; hydrogen atoms, riding model, fixed isotropic U; number of parameters refined, 380; final R indices[23](obs.data), R=8.74%, Rw 9.23% ; goodness -of - fit [24], 1.39

The crystal selected for data collection was mounted in the 198 K cold stream of a syntex $P2_1$ diffractometer equipped with a locally-modified LT-1 low temperature apparatus. A linear decay of 7.2% in the intensities of two standard reflections was observed during the course of data collection, and the data were scaled to correct for the observed decay. This decay could be attributed to the tendency of the crystals to crack and eventually to shatter when cooled below ca. 140 K. the structure was solved by direct methods in the space group P1 and refined by full-matrix (based on F) least squares. Hydrogen atoms were added at calculated positions and refined using a riding model and isotropic U's equal to 0.04 $Å^2$. This hydrogen is involved in hydrogen bonding to the neighboring oxygen, O(3). The structure also contains a small isolated electron density which could not be assigned to part of the main molecule (Figure). It is clearly larger than hydrogen, but smaller than oxygen. In order to obtain smooth convergence to 15%. A distance to chlorine of 3.08 Å places in the category of a water molecule weakly hydrogen bonded to chlorine. No absorption correction was performed. Non-hydrogen atoms were refined with anisotropic thermal parameters. A final map displayed no significant residual density. The bond angles, bond lengths and H-atomic coordinates ($x10^4$) and isotropic displacement coefficients ($Å^2$ x 10^3) are listed in tables 1 , 2 and 3, respectively.

2,3,5-Tribenzoyl-4-(2-bromobenzoyl)-1-phenylcyclohexanol (3a):

Crystallization of the crude product from glacial acetic acid gave 4.2 g , (63 %), mp 214-216° C.

IR (KBr): ν = 3550 (OH), 1660-1680 cm^{-1} (C = O).

^1H NMR ($CDCl_3$): δ = 1.54-1.79 (dd, 2H, J_{fg} =13.0, J_{ef}= 13.5, J_{eg} = 3.5, H_f, H_g), 3.44-4.24 (m, 5H, H_{b-e} and OH), 7.21-8.26 (m, $24H_{arom}$). Anal. Calcd. for $C_{40}H_{31}O_5Br$: C, 71.54; H, 4.65; Br, 11.90; Found C, 71.39; H, 4.61; Br, 11.75

2,3,5-Tribenzoyl-4-(4 bromobenzoyl)-1-phenylcyclohexanol (3b):

Crystallization of the crude product from glacial acetic acid have 3.9 g, (58 %), mp. 218-220° C.

IR (KBr): ν = 3570 (OH), 1650-1680 cm $^{-1}$ (C = O).

^1H NMR (CDCl3): δ = 2.15-2.29 (dd, 2H, J_{fg} =13.1, J_{ef}= 13.3, J_{eg} = 13.4, H_f, H_g), 4.78-5.19 (m, 5H, H_{b-e} and OH), 7.03-8.00 (m, $24H_{arom}$). Anal. Calcd. for $C_{40}H_{31}O_5Br$: C, 71.54; H, 4.65; Br, 11.90; Found C, 71.42; H, 4.60; Br, 11.82.

2,3,5-Tribenzoyl-4-(4-flourobenzoyl)-1-phenylcyclohexanol (3c):

Crystallization of the crude product from glacial acetic acid gave 4.0 g, (66 %), mp 233-235° C.
IR (KBr): ν = 3550 (OH), 1670-1690 cm^{-1} (C = O).
^{1}H NMR (CDCl$_3$): δ = 2.16-2.31 (dd, 2H, J_{fg} =13.0, J_{ef}= 13.4, J_{eg} = 3.5, H$_f$, H$_g$), 4.64-5.24 (m, 5H, H$_{b-e}$ and OH), 6.75-8.00 (m, 24H$_{arom}$). Anal Calcd. for $C_{40}H_{31}O_5F$: C, 78.67; H, 5.12; F, 3.11; Found C, 78.67; H, 5.12; F, 3.03.

2,3,5-Tribenzoyl-4-(4-chlorobenzoyl)-1-phenylcyclohexanol (3d):

Crystallization of the crude product from glacial acetic acid gave 3.5 g, (59 %), mp 220-222° C.
IR (KBr): ν = 3565 (OH), 1670-1685 cm^{-1} (C = O).
^{1}H NMR (CDCl$_3$): δ = 2.12-2.35 (dd, 2H, J_{fg} =13.2, J_{ef}= 13.4, J_{eg} = 3.3, H$_f$, H$_g$), 4.57-5.19 (m, 5H, H$_{b-e}$ and OH), 6.97-8.01 (m, 24H$_{arom}$). Anal. Calcd. for $C_{40}H_{31}O_5Cl$: C, 76.61; H, 4.98; Cl, 5.65; Found C, 76.53; H, 4.92, Cl, 5.60.

2,3,5-Tribenzoyl-4-(2,4-dichlorobenzoyl)-1-phenylcyclohexanol (3e):

Crystallization of the crude product form glacial acetic acid gave 4.2 g, (64 %), mp 224-226° C.
IR (KBr): ν = 3555 (OH), 1650-1675 cm^{-1} (C = O).
^{1}H NMR (CDCl$_3$): δ = 2.15-2.29 (dd, 2H, J_{fg} =13.1, J_{ef}= 13.3, J_{eg} = 3.5, H$_f$, H$_g$), 4.42-5.28 (m, 5H, H$_{b-e}$ and OH), 6.97-8.02 (m, 24H $_{arom}$). Anal. Calcd. for $C_{40}H_{30}O_5Cl_2$: C, 72.62; H, 4.57; Cl, 10.72; Found C, 72.59; H, 4.52; Cl, 10.69.

2,3,5-Tribenzoyl-4-(2,5-dichlorobenzoyl)-1-phenylcyclohexanol (3f):

Crystallization of the crude product from glacial acetic acid gave 3.6 g, (55 %), mp 235-237° C
IR (KBr): ν = 3600 (OH), 1660-1680 cm^{-1} (C = O).
^{1}H NMR (CDCl$_3$): δ = 2.09-2.26 (dd, 2H, J_{fg} =13.0, J_{ef}= 13.4, J_{eg} = 3.3, H$_f$, H$_g$), 4.54-5.30 (m, 5H, H$_{b-e}$ and OH), 6.93-8.04 (m, 24H$_{arom}$). Anal.Calcd. for $C_{40}H_{30}O_5Cl_2$: C, 72.62; H, 4.57; Cl, 10.72; Found C, 72.54; H, 4.53; Cl, 10.65.

2,3,5-Tribenzoyl-4-(3,4-dichlorobenzoyl)-1-phenylcyclohexanol (3g):

Crystallization of the crude product form glacial acetic acid gave 3.9 g, (59 %), mp 236-238° C.
IR (KBr); ν = 3550 (OH), 1665-1680 cm^{-1} (C = O).
^{1}H NMR (CDCl3): δ = 2.12-2.36 (dd, 2H, J_{fg} =13.1, J_{ef}= 13.4, J_{eg} = 3.5, H$_f$, H$_g$), 4.56- 5.16 (m, 5H, H$_{b-e}$ and OH), 6.97-7.99 (m, 24H$_{arom}$). Anal. Calcd. for $C_{40}H_{30}O_5Cl_2$: C, 72.62; H, 4.57; Cl, 10.72; Found C, 72.56; H, 4.55; Cl, 10.68.

2,3,5-Tribenzoyl-4-(3,4-dimethoxybenzoyl)-1-phenylcyclohexanol (3h):

Crystallization of the crude product from glacial acetic acid gave 4.5 g, (69 %), mp 207- 209° C.
IR (KBr): ν = 3600 (OH), 1660 -1685 cm^{-1} (C = O).

^{1}H NMR (CDCl$_3$): δ = 2.26-2.31 (dd, 2H, J_{fg} =13.2, J_{ef}= 13.3, J_{eg} = 3.4, H$_f$, H$_g$), 3.69 (s, 3H, -OCH$_3$), 3.77 (s, 3H, OCH$_3$), 4.71-5.01 (m, 5H, H$_{b-e}$ and OH), 6.55-8.02 (m, 24H$_{arom}$). Anal Calcd. for $C_{42}H_{36}O_7$: C, 77.27; H, 5.56; Found C, 77.15; H, 5.50.

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23. $R = \Sigma||F_o| - |F_c|| / \Sigma|F_o|$ $\qquad Rw = \Sigma\, ||F_o| - |F_c||\sqrt{w} / \Sigma|F_o|\sqrt{w}$
24. Goodness-of-fit = $[\Sigma(w \bullet ||F_o| - |F_c||^2) / (M-N)]^{1/2}$ where M is the number of observed reflections and N is the number of parameters refined.

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